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KJELL-OTTO AF KLERCKER

in memoriam

Dr. Kjell-Otto af Klercker, professor of pediatrics and practical medicine at Lund University, died on the 8th of July 1959. Born in 1871, he became professor emeritus as early as 1936.

In 1898 when Lund's Lasarett still stood in need of a children's hospital, af Klercker began his special studies of childhood diseases in the Pediatric Out-Patients' Department. In 1900, when the Children's Hospital, which had been created by private initiative under the guidance of faculty members, was finally opened, af

Klercker returned as its first assistant and resident physician. Post-graduate studies in the leading clinics of Czerny in Breslau and Thiemich in Vienna provided him with a solid foundation which was further reinforced by subsequent studies in Berlin and Leipzig. His doctor's dissertation materialized during several years of training in the Lund medical clinics and in 1905 he was offered a lectureship in practical medicine which was extended in 1909 to include pediatrics. As a result of repeated appeals to continue the professorship in

practical medicine and pediatrics, he accepted the professorship in both subjects in 1916.

The above-mentioned data already suggest the dawn of a new era in the care of sick children and in children's welfare organizations throughout our country. Thus it was the privilege of af Klercker not only personally to experience and actively to contribute to the complete liberation of pediatrics from internal medicine but also to assist in the creation of special wards for the sole treatment of children, something which at that time was entirely confined to the metropolitan area of Sweden. It may even have happened that his own solidly founded scholarship in the mother discipline was occasionally laid aside in deference to his dominant interest: children.

This interest also pervaded his scientific work. This was ushered in with a publication in 1903 on the principles of the artificial feeding of infants. It was temporarily interrupted by a study of pentosuria and creatine-creatinine and a work on the action of opium in diabetes mellitus. Again it was continued with publications on pediatric casuistics and other works in various pediatric sectors. Typical and highly illustrative of the clinician's clearness of vision was a paper dealing with nervousness in children, which as early as 1911 revealed the pediatrician's natural attitude towards and understanding of a field that not until a much later date became generally adopted by expert psychologists and psychiatrists. That this attitude was not purely accidental was clearly demonstrated when af Klercker published in 1915 a series of similar studies on neuropathic diathesis and its connection with infant nutritional disorders. This

was followed up in 1927 with a work on psychopathies in childhood, and finally in 1939 with the publication on "Childhood psychoses with special reference to therapeutic possibilities"—a subject which only nowadays is attracting attention in our country. In addition to these interests af Klercker also furthered the clinical work by means of laboratory methods, particularly within the clinical sector. The major interest was devoted to the significance of Ca- and P-ions in spasmophilia and rickets. Our knowledge of these disorders was enriched by a series of publications from his hand—his pupils also contributed—which reputedly made the Lund material one of the most highly regarded in the world.

It was only natural that these penetrating and dedicated clinical studies of children should bring af Klercker into contact with social problems. Environment played such an important role. Within this field, also, he became actively involved as one of the founders of the Children's Welfare Association in the province of Scania and as attending physician at the Admission Home and the Home for Unmanageable Psychopathic Children, both of which were connected with the University Clinic.

As clinical chief, af Klercker set a splendid example to others in the never failing interest he displayed towards both patients and younger assistants alike. He never demanded more from others than what he was willing and able to carry out himself. He welcomed suggestions and interrogations, treating them critically but always sympathetically. All could speak freely in his presence. His assistant physicians could always rely on his loyal sup-

port; his profound knowledge and varied experience were freely placed at their disposal; and more often than not he closed the discussion with some humorous remark.

We who had the pleasure and privilege of being associated with him marvelled at his genuine humility, his freedom from intrigue, his contempt for double-dealing. His attitude was that of an upright, absolutely fearless colleague. It was not always his lot to be able to choose time and place when compelled to speak his mind in the presence of all and sundry. For he never upbraided man as such; only his opinions and mode of action were subjected to criticism. When the clash was over, he would more often than not burst into

contagious laughter, declaring that perhaps he had "pitched in" a little too violently, and thereupon continue his round of the ward as if nothing had transpired. Intensely loyal to his country, to its people and to those in authority, he nevertheless took an especial pride in his Scanian birth. This deep-rooted local patriotism often occasioned a smile, but do not all true sentiments spring from the paternal hearth?

Destiny willed that he should spend all his working life in his beloved province of Scania, a knight sans peur et sans reproche. With gratitude we treasure his memory and that of his lifework.

Sture Siwe

From the Children's Hospital, Fuglebakken, Copenhagen (Chief: A. Rothe-Meyer, M. D. †), the Roentgen Department (Chief: E. de Fine Licht, M. D.) and the Department of Pediatrics (Chief: P. Bræstrup, M. D.), Copenhagen County Hospital, Gentofte

Radiographic Follow-Up in Hypertrophic Pyloric Stenosis¹ (After Medical and Surgical Treatment)

by O. STEINICKE and M. ROELSGAARD

In the acute phase of hypertrophic pyloric stenosis (hyp. pyl. sten.) the stomach presents a well-defined radiographic picture, characterized by a constantly narrowed prepyloric portion with no peristalsis over a length of 15 to 25 mm. Dilatation and delayed emptying of the stomach are not always present (4, 5, 17). It is a well-known fact that radiographic changes in the stomach persist after clinical cure of pyl. sten. They consist of a constant, more or less pronounced narrowing of the prepyloric region. Such changes have been demonstrated by Wallgren (1937), Runström (1939), and Andresen (1940). These investigators have noticed that the radiographic changes decrease with advancing age, in other words, that progressive normalization takes place during the years of childhood. Runström is of the opinion that a final normalization of the prepyloric portion is obtained in all cases about the age of puberty. Steinicke Nielsen & Roelsgaard (1956), on the other hand, by

examining 45 adults with a history of hyp. pyl. sten. demonstrated sequelae in the stomach in about 78 per cent. These results being inconsistent with those of the above mentioned investigators, we have submitted a greater number of patients to X-ray examinations through childhood. These patients had all been treated medically or surgically for pyloric stenosis in early infancy.

Material

The series under review was collected in the following manner. During the period 1935–1951 240 children had been discharged from the Children's Hospital, Fuglebakken (B.p.F.) with a diagnosis of hyp. pyl. sten. Between 1946 and 1951, 98 children were discharged from the Copenhagen County Hospital, Gentofte (K.A.S.G.) with the same diagnosis. The case reports of these 338 children have been reviewed. In 46 cases the diagnosis was so uncertain that these were excluded from the study. Sixteen of the patients had died, six of them in the acute phase. Twohundred and seventy-six patients were left for follow up study. It was impossible to get radiographic follow-up in 34 cases (address not available: 6, abroad: 9,

¹ The present work was supported by a grant from the P. Carl Petersen Fund and "Froken P. A. Brandts Legat".

refused examination: 16, pregnancy: 1, perforated ulcer: 1, mental illness: 1). The remaining 242 patients were used in the study.

Further, 13 patients were included who had been admitted in the acute phase to the B.p.F. or the K.A.S.G., but outside the stated periods; or who had had the diagnosis made in other paediatric units than the two stated above.

Thus, a total of 255 individuals with previous hyp. pyl. sten. were followed up. As shown in Table 1, 81 had been treated sur-

TABLE 1. *The starting series, classified according to method of treatment and sex.*

Treatment	Number		Total
	Boys	Girls	
Surgical	71	10	81
Spasmolytic	140	34	174
Total	211 (83 %)	44 (17 %)	255 (100 %)

gically and 174 medically (with antispasmodics). The sex incidence is likewise shown in Table 1. It corresponds exactly to the usual one of about 80 per cent boys. Fig. 6 illustrates the age distribution.

With the exception of 12 patients, examined 1954-1955, the follow-up examinations were carried out during the period from the middle of 1956 to the middle of 1958. X-ray photos were taken of the stomach and duodenal cap during fluoroscopy after administration of a contrast medium. Most of these examinations were performed ambulatorily. About 50 patients were examined in the K.A.S.G. by Dr. Roelsgaard, and about 200 were examined by Dr. Steinicke, the great majority in the B.p.F., but 18 in different local hospitals about the country.

A control group comprising 100 children was examined to obtain an estimate of the prepyloric region among children with no history of pyloric stenosis. To avoid any form of selection, this control series was collected as follows: We studied the radiographs of the stomachs of all the children

X-rayed since January 1, 1956 because of intestinal colic while staying in the B.p.F. We continued thus, until 100 cases (42 boys and 58 girls in the age group 2-13 years) were available. No consideration was given to age and sex, nor to the character of the dyspeptic complaint. None were stated to have had hyp. pyl. sten.

Results

In two out of the 255 cases of previous hyp. pyl. sten. the radiographs were of such poor quality that they were discarded.

One of these patients was a boy treated surgically, who was followed up at the age of 7; but the pictures afforded no basis for assessing the state, owing to the presence of large quantities of food residue in the stomach. The other was a boy treated medically and followed up at the age of 6. During the examination he developed excessive urticaria and Quincke's oedema, necessitating interruption before radiographs could be taken of the duodenal cap.

The results of radiography of the stomachs of 253 individuals with previous hyp. pyl. sten. (80 treated surgically and 173 medically) were assessed.

We calculated the incidence of radiographically demonstrable sequelae of hyp. pyl. sten. (seq. hyp. pyl. sten.). The criteria for regarding an X-ray finding as a seq. hyp. pyl. sten. were the same as in a previous work (16):

1. Abrupt transition from the proximal portion of the antrum to the distal 1-3 cm of the prepyloric region.
2. Persistent narrowing of this region even at maximum filling.
3. Reduced or arrested peristalsis in this region.

It must be remarked, however, that the degree of filling of the prepyloric portion,

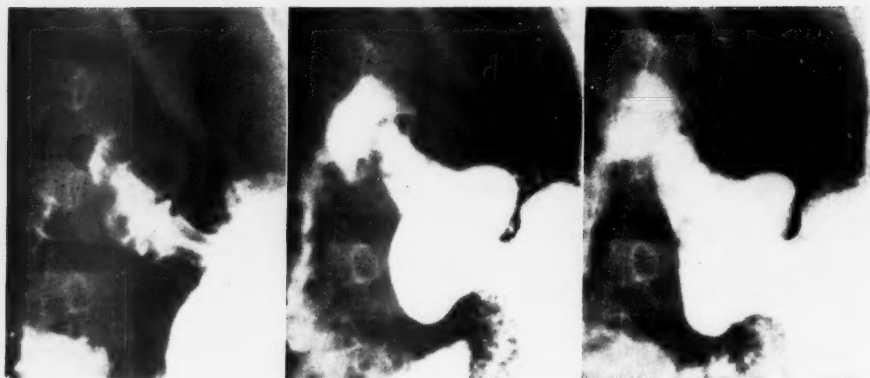


Fig. 1. (B 32). 6-year-old boy with previous hyp. pyl. sten. Pylorotomy at the age of 5 weeks. Since in good health. The X-ray photos show marked narrowing of the prepyloric region. No signs of ulcer.

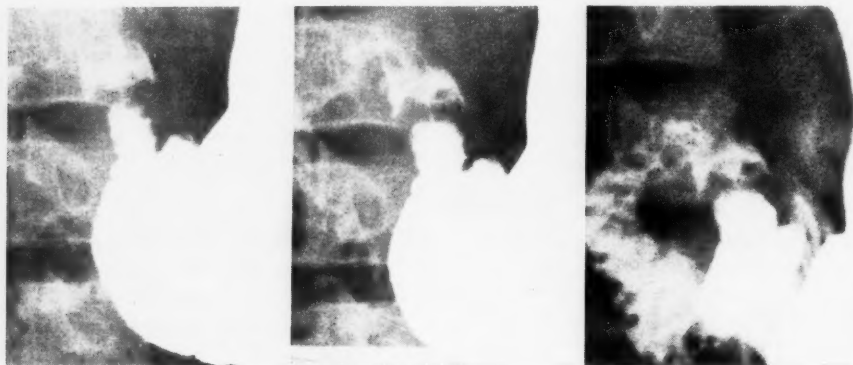


Fig. 2. (B 109). 9-year-old boy with previous hyp. pyl. sten. Treated with eumydrin. The X-ray photos show marked narrowing of the prepyloric region. Pronounced impression at the base of the duodenal cap. No signs of ulcer.

and consequently the width of the narrowed area, varies in the individual case. Figs. 1, 2, and 3 represent instances of this. In spite of such variations, these cases are always easily distinguishable from cases with normal filling of the prepyloric portion (Fig. 4). Borderline cases are more difficult to assess. Here adequate filling of the prepyloric portion is seen, except for a flattening of the distal $\frac{1}{2}$ –1 cm on the

side of the lesser curvature and abrupt transition to the superadjacent region (Fig. 5) demonstrable in all the pictures. Such cases probably also indicate sequelae of pyl. sten. As, however, the findings cannot be said with certainty to be pathological, cases of this kind will be classified as normal.

In Fig. 6 the material is divided according to mode of treatment (surgical or



Fig. 3. (B 237). 19-year-old man with previous hyp. pyl. sten. Treated with atropine. Since in good health. The X-ray photos show pronounced narrowing of the prepyloric region. No signs of ulcer.

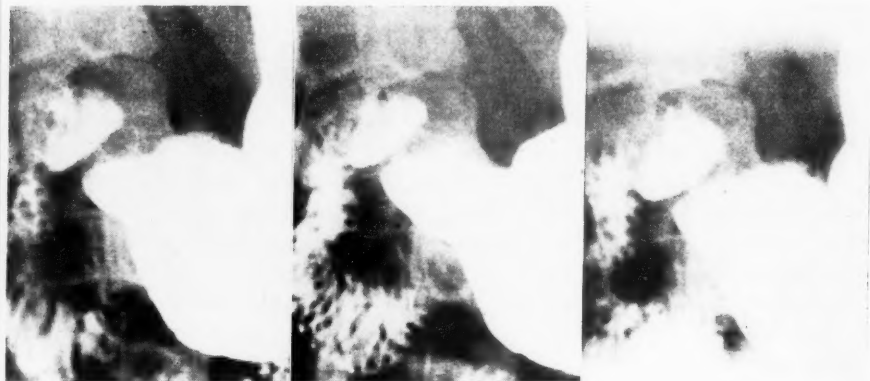


Fig. 4. (B 79). 10-year-old girl with previous hyp. pyl. sten. Pylorotomy at the age of 6 weeks. Since in good health. The X-ray photos show varying and completely normal filling of the prepyloric region. No signs of ulcer.



Fig. 5. (B 102). 9-year-old boy with previous hyp. pyl. sten. Treated with scopyl. Since in good health. The X-ray photos show a constant depression in the lesser curvature about $\frac{1}{2}$ cm from the pylorus, as well as slight flattening of this distal portion of the lesser curvature. No signs of ulcer.

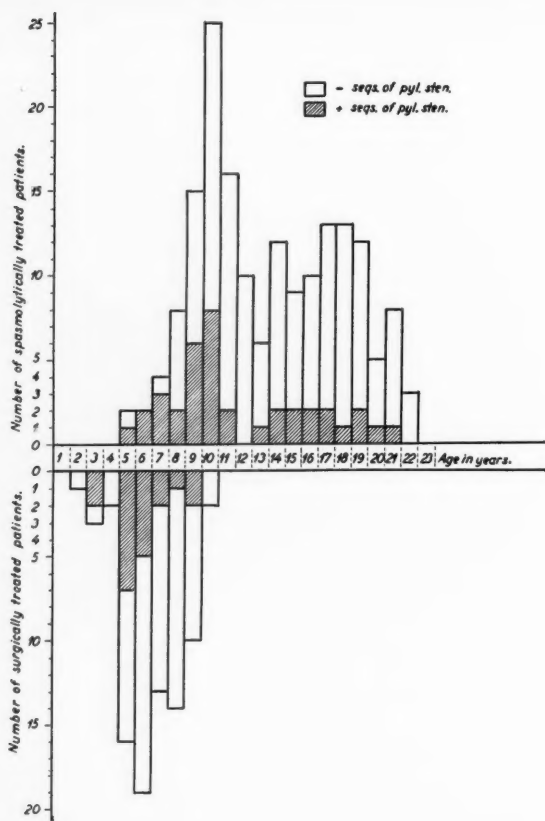


Fig. 6. Age incidence of patients with previous hyp. pyl. sten. The chart also records the X-ray findings showing sequelae of pyl. sten. Above the spasmodically treated and below the surgically treated.

medical), and according to age at examination. Within the individual age groups are stated the number of cases in which radiography revealed seq. hyp. pyl. sten., as well as the number where normal conditions were found. The chart shows the relatively greatest number of cases with sequelae in the youngest age groups.

To be able to assess the influence of age on the radiographic findings the series in Table 2 is divided into age groups within

each of the two methods of treatment. The surgically treated cases have been divided into two age groups; from 2 to 6 years and from 7 to 10 years respectively. These two groups are of the same order of magnitude. There were found 34 and 13 per cent respectively with signs of seq. hyp. pyl. sten. The medically treated patients have been divided into three age groups: 5-10, 11-16, and 17-22 years. These are likewise of the same order, and

TABLE 2. *Patients with previous hyp. pyl. sten., classified in age groups. Above the surgically treated, below the spasmolytically treated; with indication of X-ray findings suggesting sequelae of hyp. pyl. sten.*

Treatment	Age in years	Number of cases	X-ray findings		
			+ seq. hyp. pyl. sten.	- seq. hyp. pyl. sten.	% with seq. pyl. sten.
Surgical	2-6	41	14	27	34 %
	7-10	39	5	34	13 %
Spasmolytic	5-10	56	22	34	39 %
	(7-10)	(52)	(19)	(33)	(37 %)
	11-16	63	9	54	14 %
	17-22	54	7	47	13 %

here there were found 39, 14, and 13 per cent respectively with sequelae. To get an age group among the medically treated which is direct comparable with one of the surgical groups, a subgroup of 7- to 10-year-old children is presented in Table 2. A comparison showed that within the same age group the incidence of sequelae was lower among the surgically treated (13 per cent) than among the medically treated (37 per cent).

The stated noncharacteristic changes, manifesting themselves by constant depression and flattening of the lesser curvature over the most distal area of the prepyloric portion (Fig. 5), are not included in the present report. Such mild changes were so frequent in the series under review that they are probably also to be regarded as a reminder of the disease in early infancy. They were demonstrated in 11 surgically treated and 30 medically treated patients. By including these doubtful cases under seq. hyp. pyl. sten. a similar tabulation as in Table 2 gave a raised incidence of sequelae in all age

groups, but the ratio between the groups remained unchanged. In the surgical group there were then found 49 and 26 per cent respectively with sequelae in the age-classes of 2-6 and 7-10 years; and within the medical group 54, 33, and 35 per cent respectively in the three age classes.

In the control group the radiographs of 100 unselected children X-rayed owing to intestinal colic were reviewed. Of these, only one revealed such changes in the prepyloric portion as were characteristic in the study material. The patient was a 5-year-old boy admitted on account of protracted dyspepsia with associated vomiting. There was no history of vomiting in early infancy. The data available could not be supplemented, because the boy's mother has died. In the remaining 99 children perfectly normal filling of the prepyloric region was seen.

In addition to disclosing the presence or absence of the stated prepyloric changes, the X-ray examinations served to estimate the incidence of other pathological abnormalities in the study material as well as the controls. The cases presenting an intermediary contrast layer in the body of the stomach, indicating possible hypersecretion, were not included as pathological, these being only doubtfully so, especially in an ambulatorily examined series. In Table 3 is listed, for all the examined patients, the incidence of radiographic signs of ulcer, gastroduodenitis, and other specific changes. The significance of this tabulation is questionable, because the individual groups examined are not directly comparable. There was such a marked difference in age distribution between the surgically and the medically treated patients of the study mate-

TABLE 3. *Classification of the starting as well as the control series, with special reference to radiographic changes beyond signs of sequelae of hypertrophic pyloric stenosis.*

Starting series	X-ray findings				
	seq. pyl. sten.	peptic ulcer	gastro-duodenitis	pyloric spasm	other
Surgical treatment	+ in 19 - in 61	0 1	0 3	0 0	0 1 ¹
Spasmolytic treatment	+ in 38 - in 135	0 2	1 11	0 2	0 1 ²
Control series	+ in 1 - in 99	0 3	0 11	0 0	0 0

¹ Obs. for adhesions at duodenum.

² Malrotation of intestine.

rial that the results obtained here with regard to the incidence of gastroduodenitis afford no basis for concluding that these changes are more frequent among the medically treated children than among those surgically treated. The fact that a similar skew age distribution was also present between the entire study material and the control group is of no importance, as the latter group cannot be regarded as normal, since the children of this group were X-rayed because of dyspeptic complaints. However, in the entire study material (surgically as well as medically treated) there were found 8 per cent with radiographic signs of gastroduodenitis, or ulcer, a percentage which hardly exceeds that to be expected in a normal population with a similar age distribution. This survey is, however, of value in one respect. We can see from Table 3 that it is not the inflammatory changes in the stomach which cause the abnormalities in the prepyloric region designated as seq. hyp. pyl. sten.

In addition to the above-mentioned radiographic findings, the pictures in 14 cases of the study material showed signs of food residue in the stomach, proving that hours' fasting cannot be expected from all out-patients. These 14 patients have nevertheless been included, as they all showed normal conditions in the prepyloric region.

The great majority of the original patients were, moreover, questioned about possible present or past dyspeptic complaints. This question was answered by 69 of the 80 submitted to surgical treatment, of whom 65 said they had no dyspeptic troubles since their illness in infancy. Two have had mild abdominal pain, and two still have a tendency to fits of vomiting. One hundred and sixty-eight out of 173 medically treated patients were similarly questioned:

124 of these have had no dyspeptic troubles since infancy,

9 continued with regurgitation and vomiting during the first to second year of life,

7 have later in childhood been troubled by vomiting, 2 of these also by pain, 21 have or have had mild dyspeptic complaints in the form of epigastric heaviness or intestinal colic,

4 have been suffering from grave dyspepsia with ulcer-suspicious complaints; the radiographic follow-up revealed a pyloric ulcer in one of these,

3 had previously had gastric ulcer diagnosed and been treated for this.

Discussion

The radiographic follow-up here reported of 253 individuals with previous

hyp. pyl. sten. disclosed abnormalities in the prepyloric region in a great number of cases up to more than 20 years after cure of the acute disease. These abnormalities were of the same character as those demonstrated a few weeks or months after concluded treatment of the disease (17). They are therefore to be regarded as sequelae of the disease in infancy. In this investigation, comprising mainly surgically treated children followed up within the first few years of life, we found a decreasing tendency to recognizable sequelae with increasing age. In the stated paper instances are given of practically normal X-ray pictures of the stomachs of infants, aged 8-10 months. In the surgically treated the present follow-up showed that this tendency to radiographic normalization continues during the years of childhood. Thus, in the age group of 2-6 years 34 per cent had seq. hyp. pyl. sten., against 13 per cent in that of 7-10 years. These figures are significantly different at the 95 per cent limit ($\chi^2=3.91$ ($f=1$, $\chi^2_{0.95}=3.84$)). The difference is probably greater than demonstrated, as the age distribution in the whole surgical group is unequal. There were, for example, very few cases in the age-class of 2-4 years. Unfortunately, it has been impossible to determine whether the normalization rate continues to rise with increasing age, because in Copenhagen only a few surgically treated children have as yet exceeded the age of 10 years, while, on the other hand, only a few cases of pyl. sten. have been treated medically within the past 6 or 7 years. We therefore cannot obtain comparable groups, neither within the youngest nor within the oldest age-classes, from which to estimate the influence of the

method of treatment on the occurrence of sequelae. The only comparable age group existing is that of 7- to 10-year-old children. Among these there was found a considerably smaller number with sequelae in the surgical group (13 per cent) than in the medical (37 per cent). These figures are significantly different at the 97.5 per cent limit ($\chi^2=5.28$ ($f=1$, $\chi^2_{0.975}=5.02$)).¹ Here, too, the difference may be greater, owing to a skew age distribution. As shown in Fig. 5, the majority of those medically treated in the stated age group were 9-10 years old, whereas most of the ones surgically treated were 7-8. The result of the investigation suggests a falling incidence of sequelae during the years of childhood, both for the surgically and the medically treated children. Accordingly, the stated percentage figures for the medically treated children are lower and those for the surgically treated ones higher than they would be with an equal age distribution within the age interval in question. The investigation showed further, that the increasing tendency to normalization of the prepyloric region demonstrated in the surgical group manifests itself in the medical group too, only at a higher age. Thus, the normalization rate found for the age group 7-10 years among the surgically treated is not attained until the age interval of 11-16 years among those medically treated.

The normalization rate does not continue to rise, however, at least not in the medical group. After 16 to 22 years of observation exactly the same incidence

¹ The statistical calculations were carried out by Dr. B. Zachau-Christiansen, to whom our thanks are due.

of seq. hyp. pyl. sten. was found as in the preceding 6-year period. Increasing normalization after the age of 20-22 seems unlikely. We may thus conclude that for the children treated medically for hyp. pyl. sten. a steadily rising tendency to normalization is demonstrable until the age of puberty. After this age about 13 per cent will continue to present prepyloric abnormalities.

The pattern for the surgically treated cases is similar; except that the normalization occurs in a younger age-class. But the question whether surgical treatment gives fewer cases with persistent changes cannot, as stated, be answered on the basis of the series under review.

Comparison of these results with those of other workers shows agreement on some points, but disagreement on certain others. Wiedhopf & Brühl, as early as 1933, demonstrated radiographic changes in the stomach manifesting themselves by disturbances of motility and emptying in nine infants followed up 2-5 years after hyp. pyl. sten. Wallgren (1937) submitted 25 infants aged 1-3 years to X-ray follow-up and observed radiographic changes in all of them. Nine out of 13 children aged 4-7 years showed changes, and the same was true of four out of seven children aged 8-10. Thus, Wallgren's results agree fairly closely with ours. Though the number with radiographic sequelae was somewhat greater in Wallgren's series, there was also a tendency to normalization during the years of childhood.

Similar findings have been demonstrated by Runström (1939), in a radiographic follow-up of medically treated patients. Runström is, however, of the opinion that the abnormalities disappear in all patients about the age of puberty. Out of 107 examined children 63 were under 12 months of age. These all presented changes in the prepyloric region. The same was true of 17 in the age-class of 1-2 years. In the age-class

of 3-6 years 13 showed changes and four had normal findings. Five out of eight patients aged 7-10 years were normal; and finally, of two examined at the age of 13, one presented sequelae. Runström's conclusion that all children with previous hyp. pyl. sten. will show normal conditions of motility in the stomach after the age of puberty is not absolutely convincing on the basis of this work. However, Runström (1955) has submitted the same series of patients to another follow-up, after an observation period up to the age of 22 years. In this work Runström maintains that all the patients become normal radiographically. We disagree with Runström as regards this postulate.

Knutsson & Rudberg (1939), in a follow-up of seven surgically treated patients, aged 15 months to 7 years, found normal conditions in no more than two, aged 4½ and 5 years respectively.

Andresen (1940) has likewise submitted to radiographic follow-up a series of children with previous pyl. sten., 48 treated medically and 47 surgically. The children were followed up from 1 to 17 years after the acute illness. Among the medically treated, seq. pyl. sten. were seen in about 50 per cent before the age of 10 and in about 35 per cent after this age. In the surgical group a constant number of about 50 percent had sequelae in the various age-classes. This contrasts in some degree with our results, but in Andresen's series the age distribution within the surgical group is somewhat unequal, only ten being over 10 years of age.

Ehnert (1958), in a follow-up of 60 medically treated children, aged 1 to 12 years also found a decreasing number presenting pathological abnormalities with increasing age in childhood. As only nine of the children were over 6 years of age, this series affords no proper basis for comparison with our investigations.

Among investigations based on smaller series mention may be made of that of Agosta & Marchi (1948), who followed up 25 surgically treated patients, aged 1-11 years, and found sequelae in eight. Olmick & Weens (1949) also followed up a few surgi-

ally treated patients after different observation periods, and found morbid conditions in nearly all of them. The oldest one of these patients was 22.

A number of the stated investigations gave results agreeing with those of this study. However, in our own previous investigation (16), where we X-rayed the stomachs of 45 adults, ranging in age from 25 to 45, all with previous pyl. sten., we found 78 per cent with the characteristic prepyloric changes. This is a surprisingly high incidence compared with that in the present series of children examined. The difference seems to be accountable for by the difference in therapy in the acute phase. While all the children of the present investigation had been either operated on or treated medically with spasmolytics (scopol, eumydrin, atropine), none of the 45 adults previously followed up had received any form of treatment, beyond daily emptying of the stomach during the acute phase.

This clinicoradiographic experience should be compared with the pronounced degeneration of the intramuscular ganglion cells of the prepyloric portion demonstrable in the acute phase of pyloric stenosis (2, 6, 8, 9, 15). The ganglion cell degeneration causes disorders of innervation of the musculature resulting in changes in motility in the affected region. This disturbed motility may improve even in the acute phase of the disease, as observed by X-ray examination of young infants with pyl. sten. before and shortly after medical as well as surgical treatment. It has thus been shown that removal of the spasm, either by means of spasmolytics or by cutting through the circular muscle fibres, improves the motility, as the lumen of the narrowed region becomes wider and more variable (17). The changes in the prepyloric portion demonstrable late in childhood must also be regarded

as disturbances of motility. The improvement in motility during the years of infancy suggests that the ganglion cell degeneration has been partially reversible, at least at an early stage of the disease. This is undoubtedly due to the fact that treatment, either surgical or spasmolytic, reduces the number of cases with permanent disturbances of motility in the prepyloric region. The innervation of the muscles is, in other words, normalized more often and to a greater extent in such cases than in patients who have received no proper treatment during the acute phase.

While the results of the stated investigations indicate that the prospects of normalization and the time of its occurrence depend largely on treatment in the acute phase, the series under review allows no conclusions as to whether early operation gives a more favourable result than operation later in the acute phase. Neither has it been possible to assess whether the severity of the disease or the infant's age at onset has any influence on the course of healing.

Radiographic signs of gastroduodenitis and gastric ulcer were not definitely more frequent in the present series than in a normal population of the same age-groups. In a previously examined series (16), however, comprising adult patients with previous pyl. sten., a very high incidence of seq. hyp. pyl. sten. was found, and at the same time a high gastric ulcer rate. It therefore seems natural to relate these phenomena to each other. In the present series the incidence of persistent changes of motility is so much lower than in the previously examined series that we may be justified in expecting an essentially lower ulcer rate, too, even after another 10

to 20 years of observation. This is an additional indication for active treatment of hyp. pyl. sten. Whether by a longer observation period we shall find a difference in the ulcer rate between medically and surgically treated patients cannot be predicted as yet on the basis of the present series. Among the medically treated cases disturbances of motility were, as stated, equally frequent (13 per cent) in the age-groups of 11-16 and 17-22, suggesting persistence of changes present about the age of puberty. For the surgically treated patients we have no similar basis for comparison between two age groups. If a future follow-up of the surgical group will show a declining incidence between the ages of 7-10 and 11-16, resulting in a lower incidence of persistent changes about the age of puberty, there should be a chance of a lower ulcer rate at the adult age.

In discussing the relation of gastric ulcer to the acute phase of pyloric stenosis and its treatment, we must bear in mind, however, that in families with an increased tendency to pyl. sten. the ulcer rate is also relatively high (14).

Conclusion

The follow-up here reported showed a considerably lower incidence of seq. hyp. pyl. sten. after active medical or surgical treatment in the acute phase than that found in a previously examined series of untreated patients. After medical treatment with spasmolytics disturbances of motility in the prepyloric region will persist in about 13 per cent, as the increasing normalization demonstrated during childhood stops about the age of puberty.

Earlier normalization of the prepyloric portion has been found after surgical than after medical treatment. It is impossible to decide whether, in the long view, the surgical treatment gives fewer cases with sequelae than the medical, because the observation period is as yet too short for the surgically treated children. However the radiographic findings alone are evidence to suggest that at present pylorotomy must be the treatment of choice.

Summary

A series of 253 individuals with previous hyp. pyl. sten. (80 treated surgically and 173 medically) have been submitted to a radiographic follow-up between the ages of 5 and 22, with a view to assessing conditions in the stomach. We found a decreasing incidence of sequelae of pyl. sten. during the years of childhood. For the medically treated, the tendency to normalization seems to cease about the age of puberty, after which time about 13 per cent will have persistent radiographic changes. As the surgical group only comprises children up to the age of 10-11 years, we cannot decide as yet whether similar conditions prevail for these. But the investigation showed that the tendency to normalization starts at an earlier age in the surgical group than in the medical one.

In a control group of 100 hospitalized children X-rayed on account of intestinal colic only one revealed radiographic changes in the stomach of the kind designated as seq. hyp. pyl. sten.

Of the above 253 patients with previous hyp. pyl. sten. 8 per cent displayed radiographic signs of gastroduodenitis or ulcer

A previous follow-up of individuals with untreated pyl. sten. gave a much higher incidence of sequelae than that of the series under review. The results of the

present investigation stress the importance of early active treatment of hyp. pyl. sten. They also suggest that surgical treatment may be the treatment of choice.

Examens radiographiques de contrôle chez des malades atteints de sténose hypertrophique du pylore après traitement médical et chirurgical.

Résultats des contrôles radiographiques effectués chez 253 malades âgés de 5 à 22 ans après traitement d'une sténose hypertrophique du pylore (80 de ces malades ont été traités par une intervention chirurgicale). L'incidence des séquelles de la sténose pylorique fut moins élevée au cours de l'enfance. Pour les cas traités médicalement, la tendance au retour à la normale semble disparaître vers l'âge de la puberté après laquelle environ 13 % des malades présentent des altérations radiologiques persistantes. Comme le groupe de malades traités par une intervention chirurgicale ne comprend que des enfants jusqu'à l'âge de 10 à 11 ans, il est impossible de dire pour le moment si les conditions qui prévalent pour cette catégorie sont les mêmes. Toutefois, l'étude en question a révélé que la tendance à la normalisation débute à un âge plus précoce chez les sujets traités par une intervention chirurgicale que chez les sujets soignés par un traitement médical. Dans un groupe de contrôle composé de 100 enfants soumis à des examens radiographiques par suite de coliques intestinales, un patient présente des altérations radiologiques de l'estomac qui étaient du même type que celles que l'on qualifie de séquelles d'une sténose hypertrophique du pylore. Sur les 253 malades qui avaient auparavant souffert d'une sténose hypertrophique du pylore, 8 % présentèrent par la suite des signes radiographiques de gastro-duodénite ou d'ulcère. Une étude précédente sur un groupe de malades atteints de sténose hypertrophique du pylore qui n'avaient fait l'objet d'aucun traitement, avait fait apparaître une incidence beaucoup plus élevée de séquelles par rapport à celle relevée dans le groupe ayant fait l'objet de la présente étude. Les résultats de cette dernière font ressortir l'importance d'un traitement actif précoce des sténoses hypertrophiques du pylore et ils semblent indiquer que le traitement chirurgical doit être le traitement de choix dans ces cas.

Figura radiográfica en la estenosis hipertrófica del pílolo después del tratamiento médico y quirúrgico.

Estudio radiográfico de 253 casos de estenosis hipertrófica del pílolo (80 tratados quirúrgica-

mente) a la edad de 5-22 años. Existió una frecuencia decreciente de secuelas de estenosis pilórica durante la infancia. En los tratados médicamente la tendencia a la normalización parece cesar hacia la época de la pubertad, después de la cual en el 13 % presentaron alteraciones radiológicas persistentes. Como el grupo tratado quirúrgicamente comprende solo niños menores de 10-11 años, no es posible determinar si en éstos prevalecen condiciones análogas. Mas el estudio mostró que la tendencia a la normalización se inicia más tempranamente en el grupo quirúrgico que en el médico. En un grupo testigo de 100 niños hospitalizados, sometidos a exploración radiológica por cólicos intestinales, en uno se observaron alteraciones radiológicas del estómago del tipo designado como secuelas de la estenosis hipertrófica del pílolo. De los 253 casos con estenosis hipertrófica previa, el 8 % evidenció signos radiográficos de gastro-duodenitis o úlcera. Una revisión previa de individuos con estenosis hipertrófica del pílolo no tratada dió una incidencia mucho más elevada de secuelas que las series sometidas a estudio. Los resultados de la presente investigación subrayan la importancia del tratamiento activo precoz de la estenosis hipertrófica del pílolo, y sugieren también que el tratamiento quirúrgico debe ser el electivo.

Radiographische Nachuntersuchung bei hypertrophischer Pylorusstenose nach konservativer und chirurgischer Behandlung.

Radiographische Nachuntersuchungsstudie von 253 Fällen von hypertrophischer Pylorusstenose (80 darunter operativ behandelt) im Alter von 5-22 Jahren. Die Häufigkeit im Auftreten von Nachfolgeerscheinungen der Pylorusstenose war während der Kindheitszeit fortlaufend vermindert. Für die konservativ behandelten Fälle scheint die Tendenz zur Normalisierung um das Pubertätsalter herum aufzuhören, nach welcher Zeit ungefähr 13 % bleibende radiographische Veränderungen aufweisen. Da die chirurgisch behandelte Gruppe nur bis zu 10-11 Jahre alte Kinder enthält, ist es noch unmöglich festzustellen, ob dieselben Bedingungen auch bei diesen vorherrschen. Aber das Studium zeigte, dass die Tendenz zur Normalisierung bei der operativ behandelten Gruppe in einem früheren Alter beginne als bei der konservativen Gruppe. Bei einer Kontrollgruppe von 100 hospitalisierten

Kindern, die wegen intestinaler Kolik durchleuchtet wurden, zeigte eine radiographische Veränderungen im Magen, wie sie als Folgeerscheinungen von hypertrophischer Pylorusstenose aufgefasst werden. Unter den 253 Fällen mit vorausgegangener hypertrophischen Pylorusstenose zeigten 8% radiographische Anzeichen von Gastroduodenitis oder Geschwür. Eine frühere Nachuntersuchung von Individuen mit un-

behandelter hypertrophischen Pylorusstenose ergab eine viel grössere Häufigkeit von Folgeerscheinungen als die eben revidierte Serie. Die Resultate der gegenwärtigen Untersuchung unterstreichen die Bedeutung einer frühzeitigen aktiven Behandlung der hypertrophischen Pylorusstenose und legen es nahe, dass operative Behandlung die Methode der Wahl sei.

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Headache of Epileptogenic Nature

A Clinical and Electroencephalographic Study of 23 Children

by BENGT KARLSSON

Paroxysmal headache is a relatively common disease in children. Bille (1958) found the frequency of headache of clearly defined migrainous type to be 3.5% in Swedish children aged 7 to 15 years. Equally painful headache which does not meet all the criteria for the diagnosis of migraine is presumably just as common as migraine. This type of headache is often known as vasomotor headache or psychosomatic headache.

Paroxysmal headache, particularly migraine, has long been related to epilepsy. The older, mainly statistical publications presuppose a relationship for various reasons, including the transition from one disease to the other, the co-existence of migraine and epilepsy, and the remarkably high rate of migrainous history in epilepsy. Studies have also been published concerning a connection between migraine and cyclic vomiting in children, which latter symptom is sometimes interpreted as epileptogenic.

Electroencephalographic examination is normal in a large number of cases of paroxysmal headache and does not indi-

cate any direct connection with epilepsy. The most common anomalies are mild and of unspecific character. Occasionally, however, we find an epileptiform EEG, which is interpreted as emphasizing or verifying the relationship with epilepsy.

Several workers have interpreted headache as epileptogenic on the basis of three criteria: definite attacks of headache, EEG findings of epileptogenic character, and effectiveness of antiepileptic treatment. The headache has been labelled epileptic variant (4, 5), masked epilepsy (9), epileptic equivalent (7), autonomous epilepsy, thalamic or hypothalamic epilepsy (2), dysrhythmic migraine (11, 12) and hypersynchronous migraine (3).

Legitimate objections can be made to the foregoing widely accepted criteria for the interpretation of headache and certain other symptoms as epileptogenic. The fact that the symptoms manifest themselves as repeated attacks is in itself of no great importance. The majority of migraine patients are not regarded as suffering from an epileptogenic disturbance even though their symptoms are paroxysmal.

The so-called epileptogenic EEG findings do not constitute an absolute diagnostic criterion, as they are mainly based on a statistical correlation. That such findings are present does not necessarily indicate a

TABLE I.

Case	Sex	Age at onset of headache (yrs)	Duration of illness before the clin. examin. (yrs)	Heredo-familial circumstances			
				Headache	Vertigo	Epilepsy	Mental disturbance
1	F	11	2	Mother			
2	M	5	8			Aunt	Mother
3	F	4	2	Mother			Mother
4	M	8	2	Mother			
5	F	11	2	Mother			
6	F	10	1				
7	M	5	7				
8	F	4	9			Aunt	
9	F	12	2				Mother
10	M	6	6	Grandmother	Mother		
11	F	4	8	Father			
12	F	8	3	Grandmother	Sister		Mother
13	F	9	2				
14	F	7	2	Father	Sister		
15	M	5	2				
16	M	9	2	Mother, sister			
17	M	4	2	Father		Grandfather	
18	M	7	2	Father			
19	M	3	7	Aunt			
20	M	4	3				
21	M	6	8				
22	F	9	3	Sister			
23	M	5	5	Father		Cousin	
Total	—	—	—	13	3	4	4

connection between the EEG findings and the headache.

The effectiveness of anti-epileptic medication is claimed to confirm the epileptogenic nature of the condition. Since the true nature of epilepsy and the functioning of the anti-epileptic medication is unknown, it is not entirely correct to speak of a specific anti-epileptic treatment. The action of hydantoin, the principle drug tested, is not confined to the cerebral function, and this drug has been shown in perfusion experiments on isolated intestine to have a relaxing effect on smooth muscle (6). It should further be noted that treatment according to the double blind test principle has never been reported.

The main purpose of the present study was to elucidate, on the basis of general

clinical and electroencephalographic observations, which factors in addition to those listed above indicate the presence of an epileptogenic disorder.

Material

Twelve boys and 11 girls whose headache first appeared between 3 and 12 years of age made up the series (Table 1), which was selected on the two criteria paroxysmal headache and epileptogenic EEG findings. There was no reason to suspect an age predilection, although there appeared to be a certain concentration of cases between ages 4 and 5 years. The duration of the disease before the clinical examination varied between 1 and 9 years, the most common period being 2 years.

Heredofamilial circumstances

The heredofamilial circumstances are shown in Table 1. There were one or more cases of paroxysmal headache in the family of 13 cases. The diagnosis of migraine appeared to be justified in 8 members of these 13 families. The father of one patient (Case 17) had undergone a neurologic examination for headache and was found to have EEG changes in the left temporal region.

Three of the patients had relatives with pronounced vertigo. The mother of one (Case 10) had earlier undergone a neurologic examination for vertigo, and the EEG in her case revealed "a bilateral temporal abnormality of a certain epileptogenic nature". The vertigo in the other two families was present in the siblings, and had resulted in fainting spells on several occasions.

The epilepsy which was present in four families was of the grand mal type. The mothers in two families had mental disorders diagnosed as psychoneurosis (Cases 3 and 9). In two other cases one mother had been hospitalized for depression and the other for mental disease of not definitely classified type.

Other anamnestic data

Special attention was paid to the existence of possible cerebral lesions in the form of complicated delivery, later skull injury, or a history of meningoencephalitis.

Instrumental births were noted in two cases: one patient had been delivered by caesarean section (Case 5), while another had been delivered with forceps and had required postnatal incubator care for three days. In three cases delivery was

protracted with contractions lasting more than 48 hours (Cases 4, 7 and 21). Still another patient was born prematurely (Case 11).

Cerebral injury following concussion or meningoencephalitis was not suspected in any of the cases.

Symptomatology

The principle symptom was headache of marked paroxysmal nature. Some of the patients had relatively mild, protracted headache between the main attacks, but this was usually described as a disagreeable sensation rather than painful.

The attacks varied from several weekly to one every one or two months and seemed to increase with mental stress. Physical strain was not infrequently reported to bring on attacks. Watching the cinema or television almost invariably resulted in attacks of headache in six patients. A photogenic trigger mechanism was probable in these cases.

The attacks varied in duration from half an hour to 12 hours.

Certain prodromal symptoms were reported by 3 patients. Two patients complained of a general feeling of discomfort and occasionally announced: "It's coming now." One patient was invariably irritable and physically tired and dull-eyed before an attack.

The pain usually affected the whole head, although in some cases it was more pronounced frontally or occipitally. Three patients reported hemicrania in connection with some of the attacks.

Although headache was the dominant symptom, it was seldom the only one, and most attacks represented a complex of

TABLE 2.

Case	Nausea	Vomiting	Abdominal pain	Vertigo	Postictal sleep	Fever
1	×			×		
2					×	
3			×	×		
4				×		
5	×	×	×	×		×
6	×	×	×	×		
7				×	×	
8	×	×	×	×		
9	×		×		×	
10	×	×			×	
11	×		×			
12	×	×	×			
13	×	×	×		×	
14	×			×		
15			×	×		
16	×			×	×	
17					×	
18	×	×			×	
19	×	×			×	
20	×	×			×	
21	×		×	×	×	×
22	×			×	×	
23	×	×			×	×
Total	17	10	10	12	13	3

symptoms. The principal symptoms combined with headache are shown in Table 2. The attacks of headache were combined with nausea in 17 patients (74%), and 10 of these (43%) usually vomited, sometimes repeatedly, during each attack. Abdominal pain was present in 10 patients, spasmodic in some and dull ache in others. The site of the pain was either periumbilical or epigastric. In one or two cases the abdominal pain was sometimes almost as pronounced as the headache. The vertigo which 12 patients (52%) reported in connection with the attacks was rotary in one case and could not be clearly described in the others. In some cases it must have caused clouding of consciousness, which compelled the patient to lie down. A

postictal period of sleep of one to several hours was noted in 13 patients (57%).

Several other less common signs and symptoms were also recorded. A brief rise in temperature to above 38°C was found in 3 patients. One patient reported definite micropsia. The faces of some patients were highly flushed, others were pale or covered with cold sweat. Optic symptoms in the form of flimmer or scotoma were not reported by any of the patients.

In this connection it is important to note that loss of consciousness, presumably of the syncope type, without any direct relation to the attacks of headache, was reported by 4 patients.

Psychiatric examination

The mental condition of the patients was evaluated by a child psychiatrist, Dr I. Nylander. The result of the examinations is shown in Table 3. Neurosis was considered to be present in 11 cases and appreciable mental signs, although not neurosis, in a further 3 cases. The signs usually took the form of increased mental vulnerability, emotional instability, and in one or two cases, certain hysteroid reactions.

The most important and most common mental stress factors were considered to be broken homes, alcoholism or mental disorder in one of the parents, dyslexia and oligophrenia. It is noteworthy that dyslexia was present in not less than 7 patients.

General clinical examinations

All the patients were hospitalized for complete neurologic examination, including otoneurologic and ophthalmologic

special studies. Blood, urine and cerebrospinal fluid were analyzed. Roentgen examinations of the skull and the nasal sinuses were made in all the cases, while pneumo-encephalography was done and roentgenographic studies of the cervical spine were made in a few. These examinations revealed no information relevant to the headache.

Electroencephalographic examinations

Method and classification

The EEG's were recorded with an eight-channel Kaiser electroencephalograph. Both bipolar and bipolar placements were used. The number of electrodes (silver-silver-chloride saline pad electrodes) varied between 16 and 21. The electrodes were placed according to the 10-20 system. A resting EEG, for 20-25 minutes followed by 3-3.5 minutes of hyperventilation, was run in all the cases. All the patients were also submitted to optic activation with a photic stimulator of the Kaiser design. The photic stimulator gave blue-white flashes of a duration of 40-60 microseconds and with an intensity which, with rising frequency (4-25 flashes/second), dropped from 10 to 1 megalex at a distance of 5 centimeters. In a few cases EEG's were recorded during nembutal-induced sleep.

The tracings were evaluated by visual examination. The criteria for normal and pathologic manifestations were in general the same as those applied by Walter (10) and Gibbs & Gibbs (2). The effect of hyperventilation on these children was judged with the greatest caution. The tracings were classified in three main groups: normal, borderline and pathologic. The pathologic findings of principal interest were those of epileptogenic character.

Results

The epileptogenic EEG findings, which constituted one of the two criteria

for selection of cases in the present series, were of two different types.

One type had the character of generalized bursts of irregular, sometimes bilaterally synchronous waves of greatly increased amplitude (approximately 100-200 microvolts), usually from the slower part of the theta band or from the delta band. These slow waves were mixed with mono- or poly-spikes or sharp waves of approximately the same amplitude. This

TABLE 3.

Results of psychiatric examination (I. Nylander, M.D.)										
Case	Mental signs and symptoms				Mental stress					
	0	I	II	III	0	A	B	C	D	E
1	×							×		
2				×		×		×		
3		×						×		
4				×				×	×	
5			×		×					
6	×					×				
7			×				×	×		
8		×				×				
9				×			×	×		
10				×					×	
11				×		×				
12				×		×	×	×		
13				×					×	
14		×							×	
15		×			×					
16				×		×		×	×	
17	×				×					
18		×			×					
19				×					×	
20		×								×
21				×		×				×
22				×			×	×		×
23			×						×	
Total	3	6	3	11	4	6	5	9	7	3

Mental signs and symptoms: 0 = no signs or symptoms, I = mild signs and symptoms, II = pronounced signs and symptoms without neurosis, III = neurosis.

Mental stress: 0 = no stress factors, A = broken home, B = mental disturbance or alcoholism in father, C = mental disturbance or alcoholism in mother, D = dyslexia, E = oligophrenia.

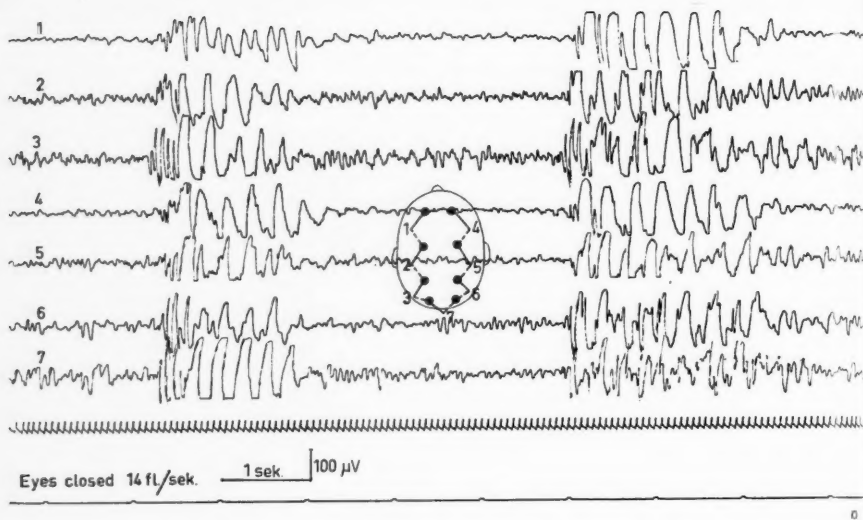


Fig. 1. Repeated discharges of irregular, multiple spike and wave activity. Eleven-year-old girl (Case 1) with paroxysmal headache for about 2 years. No epileptic seizures. Clinical symptoms successfully controlled with diphenylhydantoin.

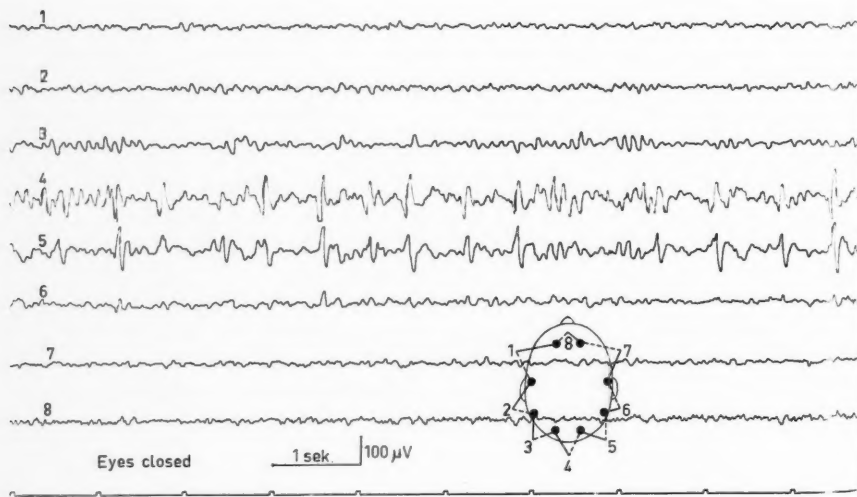


Fig. 2. Continuous spike or spike and slow wave focus in right posterior temporal and occipital areas. Ten-year-old boy (Case 23) with paroxysmal headache for about 5 years. No epileptic seizures.

activity is generally known as irregular spike and wave activity (Fig. 1).

The other type consisted of intermittent or sometimes continuous focal mono- or biphasic sharp waves or spikes of an amplitude of approximately 75–200 microvolts, sometimes combined with slow waves (Fig. 2).

Generalized bursts of irregular spike and wave activity only were seen in 12 cases. Focal seizure activity only was observed in 3 cases. Both types of seizure activity were seen in 8 patients.

The relationship between the EEG findings and the conditions of the examination appears from Table 3. Focal seizure activity was mainly seen in the resting EEG. In one case the focus was situated in the parietal region, in the others it was in the temporal, usually the frontotemporal region, but in two cases in the temporo-occipital region. Photoc stimulation was a prerequisite for the appearance of generalized bursts of irregular spike and wave activity. Photoc stimulation elicited the pathologic activity in 18 cases. Of particular interest would appear to be the fact that a temporal focus also was demonstrated in not less than 8 of those patients who responded to photoc stimulation.

Photoc stimulation also gave rise to clinical symptoms. Headache in particular, but other symptoms too, were noted in 15 of the 18 cases which gave a pathologic response to photoc stimulation. The photoc stimulation was generally terminated when symptoms developed, for humanitarian reasons. Despite this, two patients had clon- ing of consciousness, so severe that the patients did not respond when addressed, and simultaneously had mild

TABLE 4. *Electroencephalographic findings with reference to activation methods.*

	Not pathologic		Pathologic		
	Normal	Borderline	Unspecific dysrhythmia	Focal seizure activity	Generalized seizure activity
Resting	2	8	3	8	4
Hyperventilation		18			5
Photoc stimulation		3		2	18
Sleep		1		3	

muscular spasms, particularly in the arms. In still another case it brought on a grand mal seizure.

Comparative material

It is of interest at this point to report on EEG examinations with photoc stimulation carried out on 70 children who had never complained of headache and who were either completely healthy or had medical or surgical diseases which were considered to be irrelevant from the electroencephalographic point of view. In no case was the resting EEG pathologic. Nevertheless, in one eight-year-old boy with mild hemophilia, the resting EEG showed a slight unspecific dysrhythmia (borderline), while photoc stimulation gave a pathologic response in the form of short generalized bursts of irregular spike and wave activity. The possibility of an intracerebral lesion resulting from the disease cannot be eliminated, but there is little likelihood of this having been the case.

Treatment

Treatment with diphenylhydantoin (*Difhydan*, Leo) was tried in 13 cases. The

results were judged to be good in 11 of them. Of 10 patients not treated with anti-epileptic medication, 3 improved, while the condition remained relatively unchanged in the others. These observations are based on a follow-up period of at least one year after the clinical examination. The duration of the disease prior to institution of the treatment varied from 7 months to 5 years. In Case 23, psychomotor epilepsy developed 2 years after the clinical examination for headache.

Typical cases

Case 2. Boy, S.C., born in 1946. The patient's mother had unilateral paroxysmal headache. His weight at birth was 3850 g. Labor lasted more than 48 hours. Headache first appeared at the age of 8 years (1954). It took the form of marked attacks always combined with dizziness so severe as to cause the patient to lie down. The attacks occurred approximately once a week, lasted about one hour and were often provoked by visits to the cinema. Micropsia was sometimes reported. Clinical examination at the age of 10 years (1956) showed nothing of interest. Resting EEG showed generalized bursts of irregular spike and wave activity. Photoc stimulation intensified the pathologic findings, and the patient experienced pronounced discomfort with headache and clouding of consciousness. Signs of neurosis and stress factors, i.e. nervousness in the mother and dyslexia in the patient, were found (Dr. I. Nylander). Under continuous treatment with diphenylhydantoin (*Difhydan*, Leo), the patient was still completely free of signs and symptoms two years after the clinical investigation.

Case 20. Boy, L.S., born in 1950. Nothing of interest was found in the family history. The patient weighed 4700 g at birth. The birth was instrumental. The headache first appeared at the age of 4 years (1954). It took the form of pronounced attacks once or twice a month. The attacks varied in

duration from 1 or 2 up to 8 hours. The pain was most pronounced frontally and was usually combined with nausea and vomiting. There was postictal sleep for a couple of hours. There were no prodromes. No factor which definitely provoked attacks could be found. Clinical examination at the age of 7 years (1957) revealed nothing of interest but EEG showed a spike focus in the left temporal region. Psychiatric examination (Dr. I. Nylander) revealed no appreciable neurotic signs. The I.Q. was 80, according to the Terman-Merrill test. No treatment was given, and the condition remained unchanged during an observation period of 18 months after the clinical examination.

Discussion

In general pediatric practice headache of the kind described here is usually diagnosed as migraine. However, the criteria for the diagnosis of migraine in childhood are often rather vague. According to Vahlquist's (1955) rigid criteria for migraine, 12 of the cases in the present series could be labelled migraine. Vahlquist's criteria included, in addition to paroxysmal headache, at least two of the following signs: nausea, scotoma, hemiopia, and a family history of migraine.

The high rate of mental symptoms in migraine is a well-known fact. A great many mild disturbances, as well as stress factors were represented in this series. It is not unreasonable to assume that the mental disturbances are of primary importance in the headaches. It should nevertheless be borne in mind that, of those factors regarded as mental stress factors, oligophrenia and dyslexia, for example, can be assumed also to be signs of brain lesions. The mental symptoms may also be secondary to a brain lesion or a cerebral dysfunction of epileptogenic nature. In

pathologic cerebral condition of this kind is present, mental symptoms are probably more likely to appear than under normal circumstances.

The criteria for epileptogenic headache mentioned in the introduction were fulfilled by the present series. The headache appeared in well-defined attacks. EEG findings of epileptogenic character were observed in all the cases. Anti-epileptic treatment with diphenylhydantoin was considered to be effective. The rate of improvement was considerably lower in the cases not submitted to antiepileptic treatment. More extensive information would have been forthcoming had the double blind test been applied, but the series was too small for this type of investigation.

The clinical and electroencephalographic study suggested the existence of a number of other factors which could be interpreted as signs of an epileptogenic disorder.

There was a family history of grand mal epilepsy in 4 cases. An epileptogenic disturbance could also be suspected in one case in which the father had paroxysmal headache and in another one in which the mother had vertigo and was found to have focal temporal abnormalities of epileptogenic nature in the EEG.

Traumatic factors at delivery were present in 6 cases.

The headache attacks in 6 cases were reported to be brought on by watching the cinema or television. In these cases the trigger mechanism was presumably the same as in photogenic epilepsy.

In addition to the paroxysmal nature of the attacks, the clinical picture was generally characterized by a complex of symptoms. Vertigo, often leading to clouding of consciousness and postictal

sleep, suggested a cerebral epileptogenic disturbance.

Syncope not directly related to the headache in 4 cases illustrates the difficulties which may arise in differentiating attacks of unconsciousness with a cardiovascular or a cerebral background. Periods of unconsciousness as lengthy as these are often considered epileptogenic rather than of cardiovascular in origin (Livingston, 1954). Orthostatic reactions could not be shown in these patients.

The EEG findings represented marked abnormal tracings, which are generally regarded as signs of a tendency toward seizures. The fact that photic stimulation usually produced paroxysmal seizure discharges in EEG and at the same time clinical symptoms, including headache, suggests a connection between the EEG changes and the headache. The clinical symptoms were especially marked in 2 cases in which clouding of consciousness was observed and in one case in which a grand mal seizure was provoked. In one patient (Case 23) a clear psychomotor epilepsy developed two years after the examination for headache. In these cases the epileptic manifestations were obvious.

In this connection it should also be noted that the series originally consisted of 24 cases but that one case was eliminated due to a grand mal seizure during the clinical examination.

It is thus clear that there were several factors in the present material which indicated that the headache was based on a cerebral epileptogenic dysfunction. It is hardly possible to assert categorically that the pathogenesis of the headache was the same as, for example, in temporal lobe epilepsy or subcortical seizures (thalamic

or hypothalamic epilepsy), even if the EEG findings suggested a relationship with these forms of epilepsy. In short, the clinical and electroencephalographic observations do not justify extensive speculations regarding pathogenesis, but the results of the investigation appear to bear out the epileptogenic character of the headache in this material.

Summary

The present study represents an investigation on 23 children with paroxysmal headache and EEG seizure activity. Particular attention was paid to the factors which suggested an epileptogenic back-

ground to the headache, i.e., the hereditary conditions, the traumatic elements of birth, the anamnestic grounds for a photogenic causal background to the attacks of headache, the clinical complex of symptoms, and the occurrence of other signs of possible cerebral origin, e.g. syncope. The electroencephalographic studies show a noteworthy sensitivity to photic stimulation on the part of the patients. Further evidence of a causal connection between the epileptogenic EEG findings and the headache is provided by the fact that they both usually appeared at the same time under the influence of photic stimulation.

Céphalées de caractère épileptique. Etude clinique et électroencéphalographique sur un groupe de 23 enfants.

Etude d'un groupe de 23 enfants atteints de céphalées paroxystiques et présentant des électroencéphalogrammes caractéristiques d'une activité épileptique. Une attention spéciale fut accordée aux facteurs susceptibles d'établir l'origine épileptique des céphalées : conditions hérédofamiliales, traumatismes à la naissance, renseignements anamnestiques relatifs à l'influence causale éventuelle de la lumière dans la genèse des crises de céphalées, symptomatologie clinique, autres signes éventuels d'une origine cérébrale (syncopes, p.ex.). Les examens électroencéphalographiques font apparaître une sensibilité marquée des malades à l'égard des excitations lumineuses. D'autres indications révélant l'existence d'une relation causale entre les signes électroencéphalographiques épileptiques et les céphalées sont encore fournies par le fait que ce deux espèces de phénomènes survenaient d'habitude au même moment à la suite d'une excitation lumineuse.

Kopfschmerz epileptogenetischer Natur. Klinische und elektroencephalographische Studie bei 23 Kindern.

Die gegenwärtige Studie stellt eine Untersuchung an 23 Kindern mit paroxysmalem Kopfschmerz und EEG Anfallsaktivität dar. Besondere Aufmerksamkeit wurde Faktoren, welche einen epileptogenetischen Hintergrund des Kopfschmerzes vermuten liessen, gewidmet, d.i. den erblichen und familialen Verhältnissen,

den traumatischen Momenten bei der Geburt, den anamnestischen Gründen für einen photogenetisch bedingten Hintergrund für die Kopfschmerzanfälle, dem klinischen Symptomenkomplex und dem Vorkommen anderer Anzeichen von möglicherweise zerebralem Ursprung, wie z.B. Syncope. Die EEG Studien zeigen eine beachtenswerte Empfindlichkeit dieser Patienten auf Lichtreizung auf. Ein weiterer Beweis für eine kausale Verbindung zwischen den epileptogenen EEG Befunden und dem Kopfschmerz beruht auf der Tatsache, dass beide gewöhnlich zu gleicher Zeit unter dem Einfluss von Lichtreizen auftreten.

Cefalea de índole epileptógena. Estudio clínico y electroencefalográfico de 23 niños.

El presente estudio representa la investigación de 23 niños con cefalea paroxística y actividad convulsiva electroencefalográfica. Se dedicó especial atención a los factores que sugerían una base epileptógena de la cefalea, así, las enfermedades heredofamiliares, los elementos traumáticos del parto, los fundamentos anamnésticos de una causa fotógena de las crisis de cefalea, el complejo clínico de síntomas y la aparición de otros signos de posible origen cerebral, por ejemplo, síncope. Los estudios EEG muestran una notable sensibilidad a la estimulación luminica en parte de los pacientes. Ulterior evidencia del nexo causal entre las observaciones EEG epileptogénicas y la cefalea está constituida por el hecho de que ambas aparecieron al mismo tiempo bajo la influencia de la estimulación luminica.

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Unilateral Kidney Disease with Hypertension in Children

by KR. HARNÆS and M. SEIP

The importance of the kidney in the pathogenesis of arterial hypertension, especially in the presence of bilateral kidney disease, has long been known. Goldblatt's experiments in 1934, demonstrating that hypertension in dogs could be provoked by reducing the blood flow to one kidney, aroused renewed interest in the problem (5). The hypertension could be relieved by the reestablishment of normal blood-flow, or by removal of the ischemic kidney. A relation of cause and effect between kidney ischemia and hypertension seemed therefore obvious. It should be mentioned that as far back as in 1929 Ask-Upmark pointed out the occurrence of hypertension in unilateral kidney disease (1), and that 50 years ago Janeway demonstrated that constricting ligatures of renal arteries in dogs, caused a postoperative rise in blood-pressure which persisted for more than a month (10).

Goldblatt concluded from his experiments that the cortex of the ischemic kidney produced a substance, renin, which was believed to possess a pressor effect, in accordance with the earlier work of Tigerstedt & Bergmann in 1898 (23). Later stu-

dies have shown that renin is a proteolytic enzyme which splits an alfa-globulin in the plasma, hypertensinogen, leading to the formation of a polypeptide, hypertensine (angiotonin), which has an active pressor effect (2, 19). Hypertensine is rapidly removed from the blood by the action of an enzyme, hypertensinase. Hypertensine has been recovered from the blood of dogs with experimental renal hypertension as well as from cases of hypertension in man (18).—The site of formation of renin in the kidney has not been demonstrated beyond doubt. Certain findings suggest that it may be produced in the distal convoluted tubule. Tubular degeneration is the commonest and most marked histological finding in cases of renal ischemia.

The studies on renin antibodies are interesting (24). It has been possible to provoke the formation of renin antibodies in animals by the intramuscular injection of renal extracts containing renin. With this antirenin it has been possible to cure experimental hypertension in animals, but so far this has not been possible in man (7).

Relatively few cases of unilateral kidney disease with hypertension have so far been

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reported in the pediatric age group. Judging from the available literature the number of cases is approximately 60. In the course of the last two years we have seen three cases at the Children's Department, University Hospital, Oslo.

Case Reports

CASE 1. The patient was a 10-year-old girl (H.B.A.). For several years she had complained of headache, and the last 6 months before admittance her headaches became increasingly severe. A history of earlier urinary tract infections could not be obtained. Her physician discovered a severe hypertension and the patient was admitted for further study. On admittance her blood pressure was found to vary between 290/195 and 230/140. Her urine contained protein. The urine sediment was normal, except on one occasion when a few leucocytes and red blood cells were found. Blood urea and creatinine were normal. Examination of the eye-grounds showed a hypertensive retinopathy of Grade IV with papilledema and hemorrhages. A negative regitine test as well as a normal output of epinephrine and norepinephrine in the urine, excluded pheochromocytoma. X-ray examination of the heart showed changes secondary to hypertension. An excretory urography showed a small right kidney, but with relatively good excretion (Fig. 1).

A relationship between the patient's atrophic kidney and her hypertension was presumed to exist and nephrectomy was therefore performed. The kidney was atrophic, and measured $5 \times 3 \times 1$ cm. The renal pelvis and ureter were macroscopically normal. The renal artery seemed relatively narrow in comparison to the vein. The cut surface showed macroscopically normal kidney tissue in the upper half, while in the lower half the renal tissue was reduced to a narrow rim approximately 5 mm thick. In one area the renal cortex measured only 1 mm.

Histology: In the upper pole the renal parenchyma was less affected, but there

were, nevertheless, numerous hyalinized glomeruli. In the lower pole the changes were more advanced. All the glomeruli were completely hyalinized, and the arterioles and small arteries showed a marked thickening of their walls and a considerable reduction of their lumen. The tubules were atrophic. There were large hemorrhages, marked connective tissue proliferation and leucocyte infiltration in the parenchyma. The diagnosis was: atrophic and fibrous kidney with sclerosis of the small arteries and arterioles. Chronic pyelonephritis (Figs. 2a and 2b).

Postoperatively the blood-pressure fell to 180/105, and during the remainder of her stay in hospital it varied between 155/110 and 170/120. The eyeground changes receded. The proteinuria disappeared.

When seen again at the out-patient department half a year after operation, she still had a blood pressure of 170/110. She had felt well and her eye-grounds showed further improvement. Hypotensive medications was started with reserpine 0.25 mg every evening. After two months of treatment with this drug, her blood-pressure had fallen to 135/80. The treatment was interrupted, but 6 weeks later the blood-pressure had risen to 160/95. Hypotensive medication was therefore resumed and the blood-pressure fell to 135/80. The observation period is 2 years.

CASE 2. The patient was an 11-year-old boy who had previously been admitted three times to The Children's Department, twice in 1953 and once in 1954, for a hypertension, which was originally believed to be essential. He had been treated with reserpine and barbiturates, without improvement, and complained of severe headache and dizziness. He was readmitted in September 1957. His blood-pressure was then 210/130, and his urine contained protein, but was otherwise normal. Blood creatinine and urea were normal. The excretion of epinephrine and norepinephrine was not increased, and a regitine test was normal. The eye grounds showed slight hypertensive changes. Repeated excretory urograms were normal.

The patient had numerous pigmented macules and nevi. An X-ray of his thorax

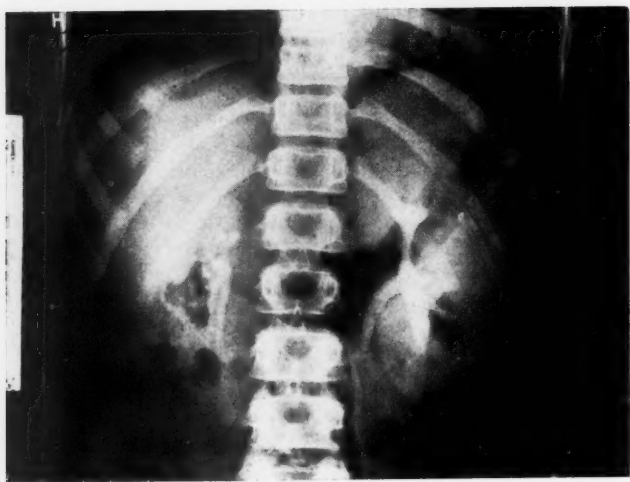


Fig. 1. Case 1: Excretory urogram. Hypoplastic kidney on the right side; relatively good excretion.

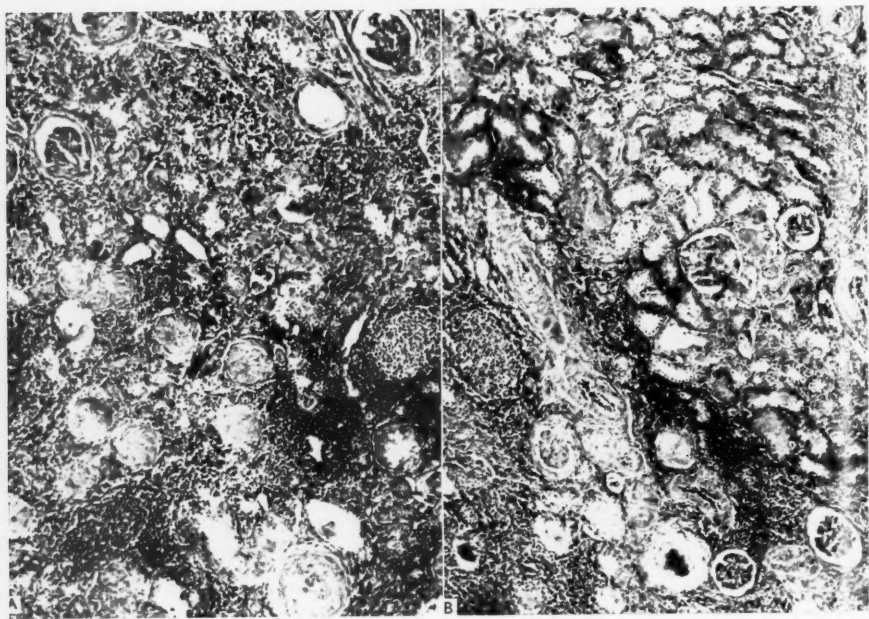


Fig. 2. a and b. Case 1. Atrophic and fibrous kidney with sclerosis of arterioles and small arteries. Chronic pyelonephritis. Haemorrhages. ($\times 60$).

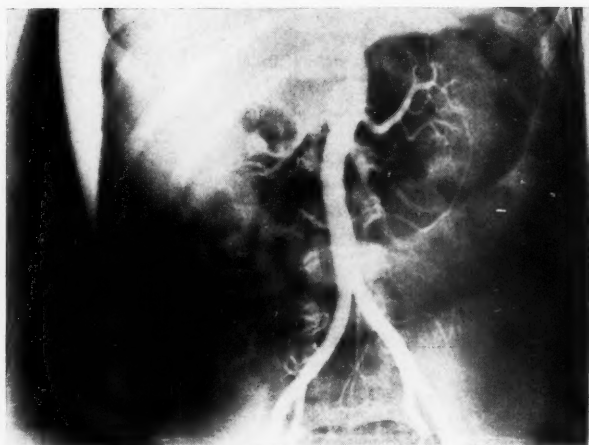


Fig. 3a, Case 2: Renal arteriogram. Narrow segment in the right renal artery and aneurysm in the renal hilus.

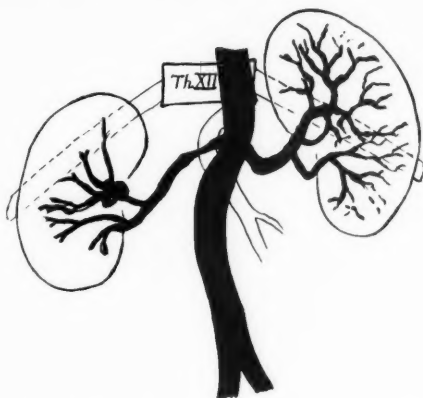


Fig. 3b, Case 2: Diagram of the renal arteriogram.

furthermore revealed a radio-lucent cystic area in the tenth right rib posteriorly.

An aortogram was carried out, and a narrow segment in the right renal artery was demonstrated. Somewhat more distally, in the renal hilus, an aneurysm of the renal artery could be seen. In addition, there was a reduction of the vascularization of the right renal parenchyma (Figs. 3a and 3b). A right nephrectomy was performed. The renal artery was tortuous and its loops constituted

almost a vascular conglomerate. In the renal hilus there was a pea-sized aneurysm.

The kidney measured $7.5 \times 5.1 \times 3$ cm. The cut surface appeared normal macroscopically. The cortex measured 6 to 8 mm. The pelvis was of normal appearance.

Microscopically the renal architecture was, on the whole, intact. In some of the glomeruli the outer layer of Bowman's capsule was thickened. There was no arteriosclerosis. The tubules showed diffuse degenerative

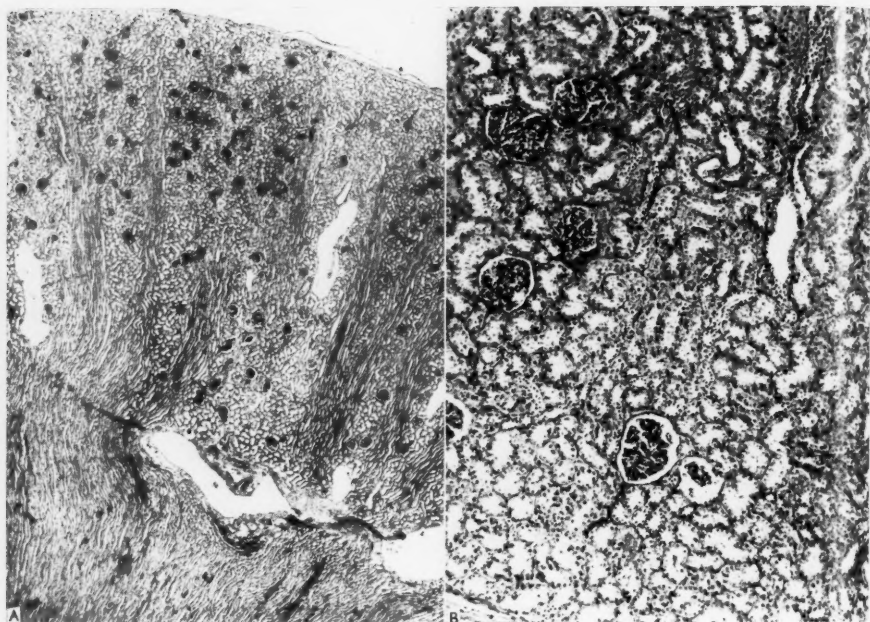


Fig. 4a and b, Case 2: Kidney with slight degenerative changes. ($\times 12$, $\times 60$).

changes, and the epithelium was swollen with poorly stained nuclei. The epithelium of the renal pelvis was of normal appearance; there was some lymphocyte infiltration of the subjacent connective tissue. The pathologist's diagnosis was: Kidney with degenerative changes (Figs. 4a and 4b).

The histological examination of the cystic radiolucent area of the tenth rib, showed a granulomatous, angiomatous giant-cell tumor.

Postoperatively the blood-pressure fell to 155/100 and by the time the patient was discharged it had fallen to 145/80. One month after operation the blood-pressure was 130/75, and after three months 115/75. There was no proteinuria and the hypertensive eye-ground changes had disappeared. One year after the operation the blood-pressure was 120/70.

CASE 3 (P.A.). The patient was a 9-year-old boy who had been well until the age of 7

when he developed enuresis. No abnormalities could be found in the urine. Two months before admittance to the Children's Department he fell ill with meningococcal meningitis, which was cured with penicillin and sulfadiazine. Under this illness the patient was found to have pyuria, as well as a fairly constant blood-pressure of 180/130. His pyuria persisted in spite of treatment with antibiotics chosen on the basis of sensitivity tests. The patient was then admitted to the Children's Department for further evaluation. On admittance the blood-pressure was 170/130, and the urine contained pus. Staphylococci and enterococci were grown from the urine. An eyeground examination showed moderate hypertensive changes in the retinal arteries. The patient seemed otherwise well. His blood-values were normal and the blood urea 34 mg%. An excretory urogram showed a left hypoplastic kidney with minimal excretion. A retrograde urography on the same side showed dilated

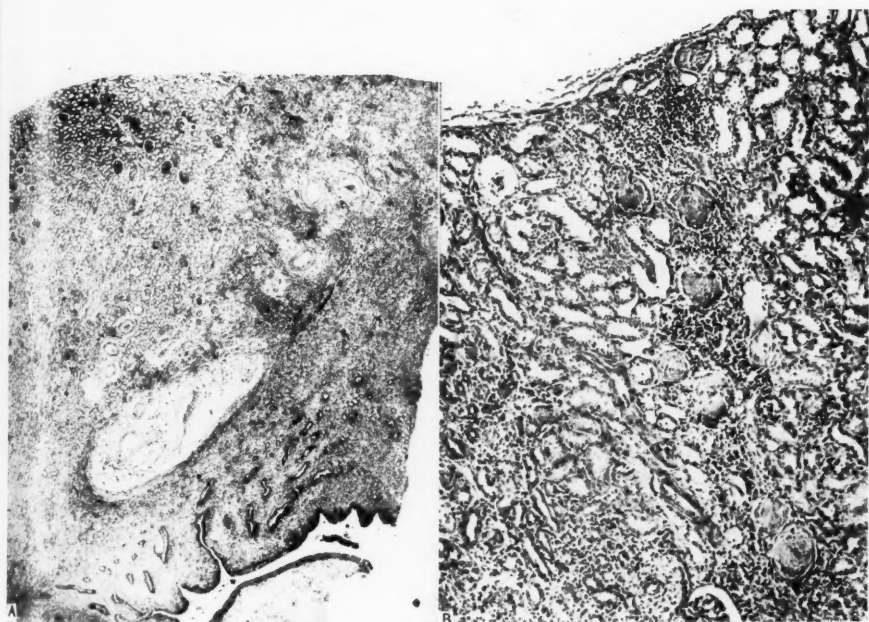


Fig. 5a and b., Case 3: Pyelonephritis. ($\times 12$, $\times 60$).

calyces and renal pelvis. Specimens obtained by catheterisation showed pus in the urine from both ureters. The patient was treated with a variety of antibiotics without any significant effect on the pyuria.

It was finally decided to perform a nephrectomy on the left side. The removed kidney was small and measured $6 \times 3 \times 3$ cm. Its weight was 25 g. The pelvis was dilated with thickening of the mucosa. On microscopical examination the renal parenchyma was found to be considerably reduced in some areas. This reduction was principally at the expense of the tubules, whereas the glomeruli were largely undamaged. In some areas, however, there was also hyalinization of the glomeruli, and in these areas there was also a considerable lymphocyte and plasma-cell infiltration, as well as some fibrosis. In the affected zones there was a hyaline thickening of the wall of the medium-sized arteries, but there was no significant arteriosclerosis. In the renal pelvis marked signs of chronic

inflammation were found. The diagnosis was pyelonephritis (Figs. 5a and b).

The blood pressure fell postoperatively to 145/95, and in the course of a few weeks it had fallen further to 110/70. The urinary infection, on the other hand, persisted for months, and disappeared only after prolonged treatment.

Three years after operation the patient was readmitted for a check-up. His blood-pressure was still normal. There was a slight pyuria which cleared up following treatment with furadantin and chloramphenicol.

Discussion

In the three cases reported severe hypertension was caused by unilateral kidney disease.

Though the clinical symptoms were, on the whole, similar in the three patients, the nature of the underlying kidney dis-

ease showed differences. In Cases 1 and 3 the pyelograms revealed hypoplastic kidneys, there were leucocytes in the urine and the histology of the kidneys showed chronic inflammation with fibrosis and marked leucocyte infiltration as well as degenerative changes, principally of the tubules. In both these cases there was, furthermore, considerable hyalinization of the glomeruli and arteriosclerosis. Whether these two cases represent a congenital hypoplastic kidney which has suffered secondary infection, or whether the primary cause has been a pyelonephritis with secondary atrophy, is impossible to decide with certainty, because in both instances the end result would be a scarred atrophic kidney. The latter possibility seems nevertheless the most probable.

The pathogenesis in Case 2 is different. Here the aortogram revealed a narrowing of the renal artery and an aneurysm in the renal hilus. These changes have led to renal ischemia and subsequent degenerative alterations, particularly of the tubules.

In all our patients degeneration of the tubular epithelium was thus a prominent finding. This has also been the experience of other authors (8, 16, 17). It is presumed that the tubules are first and most severely affected when the blood supply to the kidney is reduced, presumably because of the highly complex metabolic functions carried out by the tubular epithelium as compared to the simple filtration which takes place in the glomeruli. It has previously been mentioned that renin, the factor which initiates hypertension, is believed to be produced in the tubules.

An interesting feature of Case 2 is that, in contrast to the other two cases, arteriosclerosis could not be demonstrated.

This is in accordance with the presumption that an obstruction of the renal artery protects the arterioles of the ischemic kidney from the increased blood-pressure which would lead to the development of a malignant arteriosclerosis. In such cases, however, arteriosclerosis can develop in the other kidney, a factor which is of importance for the results following nephrectomy. In Cases 1 and 3 the primary cause of the hypertension is to be found within the kidney, and in such cases hypertension can lead to a generalized arteriosclerosis affecting both kidneys.

In the first case the blood-pressure did not drop to normal after the operation. Hypertension persisted, probably because generalized arteriosclerosis had had a chance to develop. Treatment with reserpine lowered the blood-pressure almost to normal, but it rose again as soon as the drug was postponed. On resumption of the treatment normal values were once more obtained.

Diagnosis: A fixed hypertension in childhood is almost always secondary. Primary essential hypertension in children may occur but is extremely rare (6, 12, 13). In the face of childhood hypertension an energetic search must therefore be made for the primary cause, so that adequate treatment can be instituted. Hypertension in a child can be due to many different causes e.g. coarctation of the aorta, cerebral lesions, pink disease, hormonal disturbances such as Cushing's syndrome, hyperaldosteronism and pheochromocytoma. In many cases, however, the cause is renal, and in all cases of hypertension a detailed study of the kidneys and urinary tract must be performed.

Experiences from recent years have shown that unilateral kidney disease, not altogether rarely, may be the cause of hypertension especially in children and young adults. The underlying kidney lesions may vary, but they all have in common that they lead to degenerative changes in all or part of the renal parenchyma. These lesions may belong to one of the following categories:

1. Infections: pyelonephritis, pyonephrosis, renal tuberculosis.
2. Renal artery disease or anomaly: malformations, thrombosis, embolism, aneurysm, compression of the artery, renal infarct, thrombngitis obliterans.
3. Urinary tract obstructions.
4. Renal malformations or tumors: hypoplasia, renal ectopies, renal cysts, renal tumors.

An unilateral kidney lesion may be difficult to demonstrate. Urine-analysis, renal function tests, urograms and retrograde pyelograms, will in most cases but not always, lead to a correct diagnosis. These methods can fail, especially in Group 2, where there is a disturbance of the arterial blood-supply. In these cases the aortogram is particularly helpful. In all cases of hypertension where the conventional methods fail to reveal a renal or urinary tract cause, and where no other satisfactory explanation for the hypertension is to be found, a renal angiogram should be carried out (14, 21).

The recent experimental work of Connor *et al.* (4) and White *et al.* (11) has shown that a reduced arterial blood supply will lead to a decreased urine formation in the affected kidney and that the concentration of urinary sodium and chloride will

be lower in urine from the diseased kidney than in urine from the healthy kidney. Catheterisation of the ureters and separate determinations of the sodium and chloride concentrations in the urine from both kidneys can lead to a suspicion of unilateral kidney disease earlier than if only the routine methods of urinary tract examination are employed.

Results of nephrectomy

The first optimistic reports of cases of hypertension in unilateral kidney disease which had been improved or cured by surgery were soon followed by numerous others, where the results obtained had not been so favorable.

In 1956 Homer Smith published a review of 575 cases collected from the literature, all of which had been nephrectomized (20). In 270 of these cases the blood-pressure was not influenced by the operation; 106 cases were improved; in 50 cases the blood-pressure became normal, but the patients had been followed for less than one year; 149 cases were described as cured. The total proportion of cases considered cured was therefore 26%. Smith established the following criteria for cure: A blood-pressure of 140/90 or lower, and a follow-up period longer than one year. His cases included both children and adults. Birk-Jensen & Frøjel (3) have collected 20 cases from Scandinavia, 6 of which had a normal blood-pressure 2 years after operation. Of these cases 3 were children and all were cured. Sabin (15), in 1948, reviewed 100 cases, 13 of them children. In 12 of these normal blood-pressure were obtained and the remaining child was much improved. In 1954 Schaffer & Markowitz (16) collected 30 cases in children. In 2 of these only the blood-pressure remained unchanged. In 20 (67%) the blood-pressure fell to normal, but 6 of these were followed for less than one year. In the re-

maining 8 cases there was a significant drop in blood-pressure but normal values were not obtained. Thus the prognosis is far better in children than in adults. Among adults, age appears to have little influence on the prognosis. It has been assumed that the difference in the prognosis in adults and children is due to the different duration of the hypertension in the two groups.

The reason for the failure of nephrectomy to effect a cure in some cases, can of course be that the removed kidney is not responsible for the hypertension. It is also possible, however, that the hypertension has persisted too long and that a secondary generalized arteriolosclerosis, which includes the remaining kidney, has developed. Isaacson & Wayburn (9) described a patient who died post-operatively after having been nephrectomized for an obstruction of the renal artery. These authors found vascular changes typical of a benign hypertension in the removed kidney, whereas the remaining kidney showed changes typical of a malignant hypertension. In some cases skin and muscle biopsies have therefore been taken preoperatively in an attempt to estimate the presence and degree of generalized arteriolosclerosis. Thompson & Smithwick (22) have recommended that a biopsy of the healthy kidney be taken, thus permitting an evaluation of the results to be expected from nephrectomy. They attempted this in two cases. In one case the biopsy showed a benign nephrosclerosis, whereas in the other marked vascular changes were present. Both cases were, however, cured by nephrectomy. The possibility that even marked vascular changes in the remaining kidney may be reversible would therefore seem to exist.

The duration of the hypertension prior to operation is probably of considerable importance for the prognosis. Nevertheless cures have been seen even in hypertension of long standing. Our second patient had had severe hypertension for at least 4 years before operation, and cases of cure by nephrectomy have been described

in patients whose hypertension had been present for considerably longer than this.

Marked retinal changes do not exclude good postoperative results. In all our patients the retinopathy cleared up, and in our first patient the retinopathy had been of a severe degree.

Infection or diminished function of the other kidney has been considered a contraindication to nephrectomy. In our Case 3 there were signs of infection also in the remaining kidney. It was presumed, however, that the infection could be secondary to that which was present in the atrophic kidney and that a favourable response to intensive antibiotic therapy could be hoped for. Marked reduction of renal function in the contralateral kidney must be considered as an absolute contraindication to nephrectomy (25).

Summary

Three cases of severe arterial hypertension due to unilateral kidney disease are discussed. Two of the patients had chronic pyelonephritis with secondary atrophy of one kidney. The third patient had a narrowing as well as an aneurysm of the renal artery, discovered by an aortogram. In two of the patients the blood-pressure returned to normal after nephrectomy, while in the third the addition of hypotensive medication was necessary to obtain a normal blood-pressure.

The necessity of performing an aortogram in all cases of hypertension in childhood where the etiology is obscure, is stressed. With adequate treatment, the prognosis is better in children than in adults, but it is not always good.

Néphropathie unilatérale avec hypertension chez des enfants.

Discussion de trois cas d'hypertension artérielle sévère due à une néphropathie unilatérale. Deux de ces malades étaient atteints de pyélonéphrite chronique avec atrophie secondaire d'un des reins. Le troisième présentait une sténose ainsi qu'un anévrisme de l'artère rénale qui furent décelés à l'occasion d'une aortographie. Dans deux de ces cas, la pression sanguine revint à la normale après exécution d'une néphrectomie; dans le troisième, l'administration supplémentaire d'un médicament hypotenseur fut nécessaire pour ramener la tension à un niveau normal. L'auteur met l'accent sur la nécessité de procéder à une aortographie dans tous les cas d'hypertension dont l'étiologie est obscure chez les enfants. Lorsqu'on applique un traitement adéquat, le pronostic est meilleur chez les enfants que chez les adultes, mais il n'est pas toujours favorable.

Einseitige Nierenerkrankung mit Hypertension bei Kindern.

Drei Fälle von schwerer arteriellen Hypertension, die durch eine einseitige Nierenerkrankung hervorgerufen war, werden erörtert. Zwei unter den Patienten hatten chronische Pyelonephritis mit einer sekundären Nierenatrophie. Der dritte Kranke hatte eine Verengung als auch ein Aneurysma der Nierenarterie, die mit Hilfe eines Aortogrammes entdeckt wurde. Bei zweien

dieser Kranken kehrte der Blutdruck nach Nephrektomie zur Norm zurück, während bei dem dritten eine zusätzliche Behandlung mit druckherabsetzenden Medikamenten notwendig war, um normalen Blutdruck zu erlangen. Die Notwendigkeit, ein Aortogramm bei allen Fällen von Hypertension im Kindesalter, wo die Ätiologie verborgen ist, auszuführen, wird unterstrichen. Unter entsprechender Behandlung ist die Prognose bei Kindern besser als bei Erwachsenen, ist aber nicht durchwegs gut.

Nefropatía monolateral con hipertensión en los niños.

Se discuten tres casos de hipertensión arterial grave por nefropatía monolateral. Dos de los pacientes presentaban una pielonefritis crónica con atrofia secundaria de un riñón. El tercer paciente aquejaba un estrechamiento así como un aneurisma de la arteria renal, descubierta por el aortograma. En dos de los pacientes la presión arterial se normalizó después de la nefrectomía, mientras que en el tercer caso fue necesario recurrir además a medicación hipotensiva para obtener la normalización de la presión arterial. Se insiste en la necesidad de efectuar un aortograma en todos los casos de hipertensión en niños, en que la etiología sea oscura. Con tratamiento adecuado, el pronóstico es mejor en los niños que en los adultos, aunque no siempre es bueno.

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Cysts of the Lung in Infants and Children

by S. BRÜNNER, P. THUE POULSEN and J. VESTERDAL

Cysts of the lung in infancy and childhood present an interesting problem which involves differential diagnostic difficulties. Often, the clinical appearances are exactly identical with those of other pulmonary diseases, and the differential diagnosis can be made only by radiography.

It must be realized at once that the nomenclature relating to cyst-like structures of the lung is comprehensive and confusing. There are no less than 28 names for cyst-like cavities of the lung (17, 20). Among the most common designations are pulmonary cysts, bronchogenic cysts, congenital cystic disease of the lung, pneumocysts, honey comb lung, solitary and balloon cysts of the lung, and pneumatocele.

In the present paper it seemed most reasonable to use the term cyst of the lung when referring to air- and/or fluid-filled cavities originating from the lungs. In this designation we include also subpleural bullae and bronchogenic cysts, but not cylindrical or saccular bronchiectasis, tuberculous cavities, pulmonary abscesses, or parasitic cysts.

Previous Investigations

Aetiology and Pathogenesis

Whether cysts of the lung are congenital or acquired is still a matter of dispute. Cysts have been found in newborn infants and in fetuses. Wolman reported the case of a 6-month-old foetus born prematurely. Kjærgaard found cysts of the lung in a baby, born 6 weeks before term, who died 40 minutes after birth. Still, these cases appear to be extremely rare. In an autopsy material covering 22 years from the Babies' Hospital, New York, only one case was found, in a premature baby. Among 5000 autopsies Lederer did not find any case of congenital cysts of the lung. Caffey found none among 5000 newborn infants who had chest radiography on the first, second, or third day of life.

There is little doubt that a number of cases diagnosed as congenital have in fact been acquired.

Increasing activity within thoracic surgery during the past decade has resulted, among other things, in an increasing number of reports on cysts treated surgically. This has afforded a larger material as well as a possibility of a thorough study of the cysts. Today most lung cysts must be interpreted as acquired, generally caused by a valve mechanism (check valve bronchial obstruc-

tion) permitting passage of air during inspiration, but not during expiration (4, 7, 10, 11). This mechanism may be imagined to be of a functional nature, due to bronchospasm, or mechanical due to a kink in the bronchus, mucosal hypertrophy, or oblique communication of the bronchus with the region of the cyst (4, 11). The valve mechanism may cause distension of alveoli and possibly also of the distal part of the afferent bronchus or alveolar rupture. According to certain authors (int. al. 9) there is, under normal conditions, some collateral circulation of air from the affected alveoli into the surrounding pulmonary tissue, and no cyst will arise by this mechanism alone. If the pulmonary tissue around the involved area is inflamed, the air may not flow into the surroundings, and a cyst will arise. Moreover, reduced elasticity of the alveolar and/or bronchial wall may no doubt be contributory. This introduces a congenital factor into the formation of a lung cyst.

Among the acquired cysts there is a special group, transitory cysts, which some authors have called pseudocysts and others pneumatoceles (1, 21). These cysts often follow upon staphylococcal pneumonia in children. The first radiographic sign is generally a dense infiltration, frequently called pneumonitis. Within this area, the cyst arises and often disappears spontaneously. Without doubt, it is due to a sort of valve obstruction, and it seldom grows large. Caffey (5) has reported not less than 8 cases in babies younger than 6 months, where the cysts disappeared spontaneously. He concluded that cysts occurring during the first months of life are generally acquired pneumatoceles which disappear, without surgery, in the course of some weeks or months.

Pathology

The cysts may be single or multiple. They may be restricted to one area or scattered over large portions of the lung. They may be unilateral or bilateral, unilobar or multilobar. As a rule, they contain fluid or air or both. The content may also be pus or blood.

On microscopic examination they are generally lined with a tall columnar respiratory epithelium merging into flattened alveolar epithelium. Moreover, the wall shows irregular groups of elastic tissue, muscle fibres, and cartilage. This is unlike the findings in bronchiectasis in which there is usually regular stratification (4, 8). Frequently, there are smooth cystic walls despite infection (16). Formerly, it was believed that congenital cysts were lined with respiratory epithelium, whereas acquired cysts were lined with flattened endothelial cells or with no epithelium at all (6). The investigations of Caffey, Maier and Pryce, however, clearly showed that acquired cysts may often be lined with respiratory epithelium.

Signs and Symptoms

According to the literature, the cysts may be classified as follows:

- I. asymptomatic.
- II. (a) those which give rise to symptoms due to pressure on surrounding structures because of the size of the cyst or cysts,
- (b) those which give rise to symptoms due to infection.

The most common sign is a constant cough, whereas expectoration is rare, presumably because children usually swallow the sputum.

Haemoptysis is rather uncommon in children, but frequent in adults. Deformities of the chest are fairly rare, contrary to bronchiectasis. Recurrent attacks of pneumonia and febrile bronchitis in children should always arouse a suspicion of cysts of the lung or bronchiectasis, and chest radiography should be performed.

Clinically, it is often impossible to distinguish pneumonia, abscess of the lung or empyema from an infected pulmonary cyst, as all give rise to the same symptoms. The most important diagnostic aid is radiography, in the anteroposterior as well as lateral view, and tomography. Non-infected cysts generally present themselves as air-

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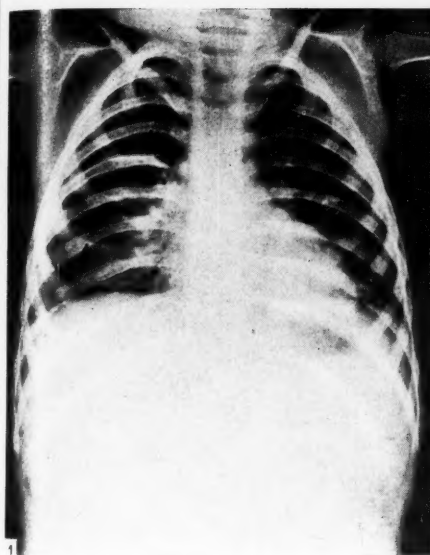


Fig. 1. A boy, aged 3½ years, with cysts in the central right lung field. Cysts discovered at the age of 3 months. Attacks of febrile pneumonia during the intervening period.

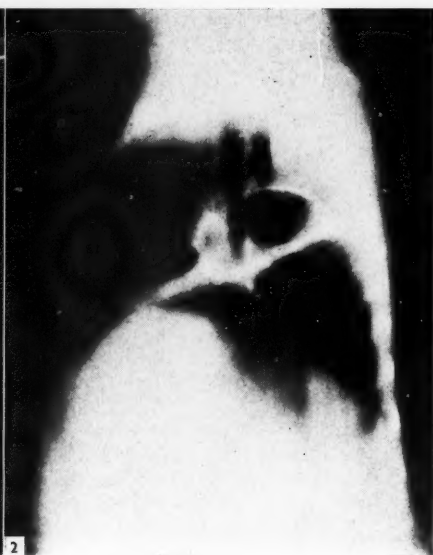


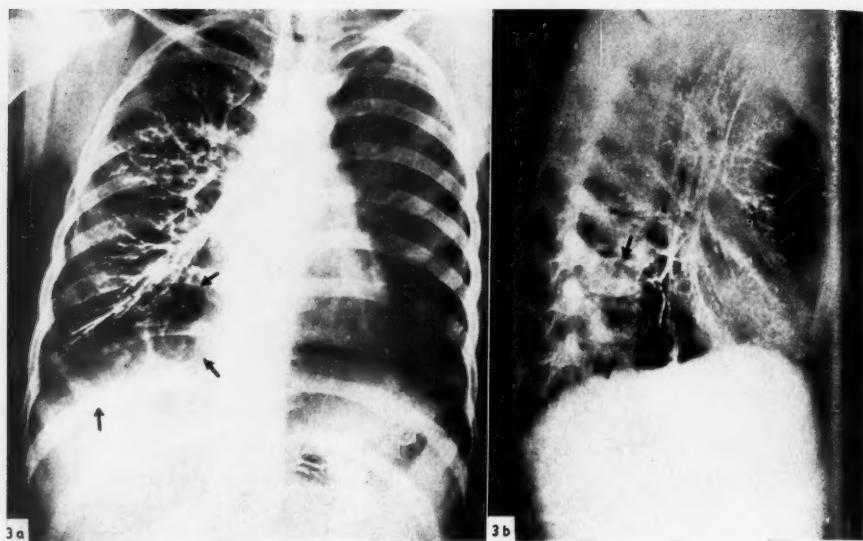
Fig. 2. Same case as in Fig. 1. Tomography showing cysts with atelectases in the surroundings.

filled or fluid-filled, regular, rounded, well-defined cavities in the pulmonary tissue.

Asymptomatic cases are often detected by chance in case finding surveys. In the area concerned, the lung markings are absent or reduced, and there is a thin demarcation against the surrounding structure, so thin that frequently it may be very difficult to discern the cystic wall proper (Fig. 1). Tomographic study or bronchography may often be employed to confirm the diagnosis (Fig. 2). On a bronchogram, the bronchial branches surrounding the cysts are displaced. Often there is deficient or no filling of the cyst due to obstructed or narrow communication with the bronchial tree (Fig. 3). Radiologically, it is impossible to distinguish between acquired and congenital cysts. The wall thickness does not give any definite information in this respect, since both kinds of cysts may be thin-walled or thick-walled. It is very important to remember that the large, expansive cysts, or balloon cysts, may

be difficult to differentiate from pneumothorax. A thin strip of lung tissue laterally indicates a cyst pressing the pulmonary parenchyma towards the chest wall, whereas in a free pneumothorax there is no lung tissue laterally. However, it is often impossible to discern the lateral demarcation even in a tangential projection. In cases of large cysts, the hilar shadow is often narrowed and elongated due to the pressure by the cyst, and there is not a collapsed lung at the root as in pneumothorax (Fig. 4).

If the cysts contain fluid, the radiographic signs are usually dense, opaque, round shadows in the lung parenchyma (Fig. 5). As a rule, these shadows are less dense than the cardiac shadow. There may be differential diagnostic difficulties, especially from abscesses, tuberculous cavities, or solid tumours of the chest, such as bronchogenic cancer, teratoma, chondroma, neurinoma, cystic neuroblastoma, or adenoma. In children, however, bronchogenic carcinoma is so rare that it



Figs. 3a and 3b. A girl, aged 10 years. Since the age of one year repeated attacks of febrile pneumonia. Bronchography shows bronchial branches by-passing cysts in the postero-basal segment, but no filling of the cysts. Operation revealed intralobar bronchopulmonary sequestration.

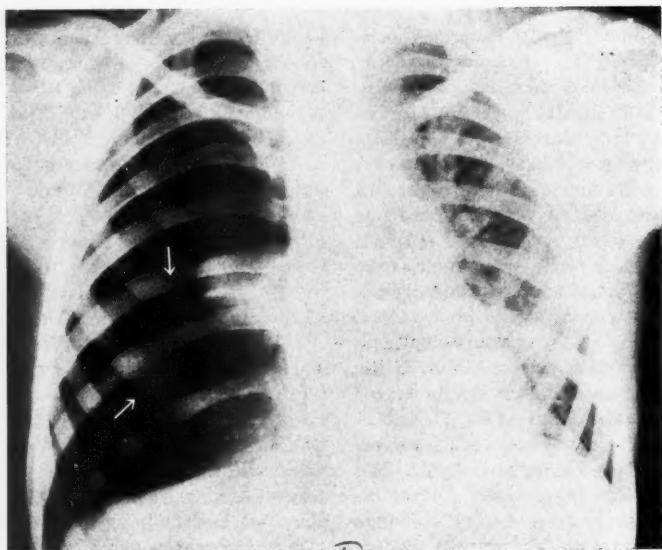


Fig. 4. A boy, aged 5 years. Symptom free until one month prior to operation, when spontaneous pneumothorax suddenly occurred. Large cyst and several small ones in the right upper lobe.

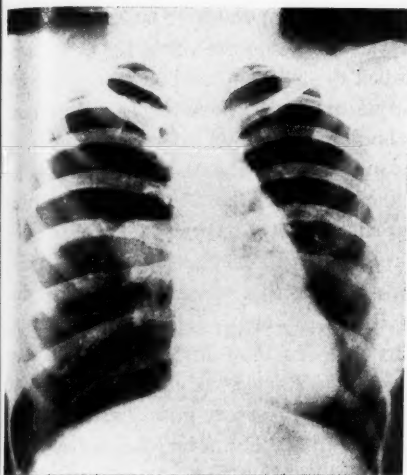


Fig. 5. A girl, aged 15 years. History of pneumonia 9 years before the operation, but no other symptoms. In the lower lobe a fluid-filled cyst, the size of a tangerine, giving rise to localized emphysema.

does not present a major diagnostic problem. Teratomas seldom occur until after puberty. Neurinomas, on the other hand, may be difficult to distinguish from fluid-filled pulmonary cysts, but a study of e.g. the intervertebral foramina may afford a hint. Infection of the lung cyst or cysts considerably increases the differential diagnostic difficulties.

Treatment

The above-mentioned check-valve mechanism which is operative in the formation of certain cysts of the lung is presumably responsible for the partially obstructed outflow from the cysts and their consequent tendency to retain bronchial secretion and infection. Recurrent infection in a cyst is the most common indication for surgery, which should aim at removing the affected segment of the lung, since each infection involves a risk of perforation of the cyst and empyema.

Preceding drainage of the cyst before its surgical removal has previously been recommended where infection is present (Maier).

If the cysts do not adhere to the chest wall, this method, however, involves a great risk of empyema and collapse of the lung, so lobectomy or resection should be preferred.

Surgical removal is indicated also in large cysts compromising pulmonary function and perhaps causing displacement of the mediastinum and the remaining lung. Cases of pneumothorax also afford a clear indication for resection, possibly preceded by drainage with suction.

In cases of small cysts, detected accidentally, which show no tendency to increase in size and which are unattended by infection, an expectant attitude is sometimes permissible, but the trend is towards operating for fear of infection.

Some authors, e.g. Korol, have mentioned the danger of bronchial carcinoma developing in the wall of the cyst. This is an extreme rarity, however, but it contributes to an active surgical attitude.

Present Investigations

The series to be presented below comprises 20 infants and children, aged 23 days to 15 years, found among 92 patients of all ages with cysts of the lung treated by operation at the Departments of Thoracic Surgery of the University Hospital, Copenhagen, during the period 1940-1957.

TABLE 1.

		0-1 year	2-5 years	6-12 years	13-15 years	Total
A	Boys	5	3	4	1	13
	Girls	2	1	4	0	7
	Total	7	4	8	1	20
B	Boys	3	3	6	1	13
	Girls	1	0	2	3	6
	Total	4	3	8	4	19

Age at onset of symptoms (A) and at operation (B).

The sex and age distribution at the onset of symptoms and at operation may be seen from Table 1. There is a male preponderance (13:7) as in other materials (12, 19, 20).

Signs and Symptoms

Cough was present in not less than 12 patients. Seven had expectoration and 7 recurrent attacks of fever indicating infection. On the other hand, there was no case of haemoptysis which is rare in children, as also stated above. Dyspnoea, due to reduced respiratory volume, was present in 7 and cyanosis in 5. Chest pain was reported in one case, probably due to pleural changes and pneumothorax.

There was a history of one or more attacks of febrile pulmonary disease in 12, while one child had had recurrent infections in a cyst erroneously diagnosed as an abscess, and one had had recurrent pneumothorax. Four patients had had symptoms for only one month prior to admission (pneumothorax in three cases and pyo-pneumothorax due to a ruptured infected cyst in one). Two had asymptomatic cysts of the lung, detected by chance, which had been followed for 2 and 10 years respectively before the admission.

One patient, a 14-year-old girl, had undergone operation for a large hiatal hernia in the same department two years previously. Another patient, a girl aged 27 days, had a severe malformation of the left hand.

Aetiology

In 4 cases operation revealed cystic changes in connection with an anomalous origin of an artery direct from the aorta

to the segment concerned. Changes of this nature were described first by Pryce who called them intralobar bronchopulmonary sequestration. Various theories have been advanced regarding the nature of such cystic structures. Recent authors are inclined to believe that the changes, vascular anomalies as well as cysts, are of congenital origin (2, 3). In one case, a cyst of the lung co-existed with a supernumerary lobe, but without any artery originating direct from the aorta. In 13 of our patients the symptoms had started, as already mentioned, as febrile respiratory infections. It is difficult, therefore, if not impossible, to decide whether the cysts were congenital and the pneumonias secondary or whether the pneumonic processes gave rise to the formation of cysts which then caused the symptoms. Two cases began as pneumothorax without preceding symptoms. Two began in babies, aged 14 and 17 days, in the form of pneumonic changes present on admission. In these cases too, it is very difficult to tell whether the cysts were congenital or acquired. One of these babies also had a congenital malformation of the hand, and both exhibited large, rather thick-walled cysts at operation. It is most likely, therefore, that these cystic cavities were congenital.

The localization is shown in Table 2.

TABLE 2.

Localization of cysts	
Right:	Left:
Upper lobe 2	Upper lobe 6
Lower lobe 6	Lower lobe 5
	Upper lobe + lingula + lower lobe 1

TABLE 3. *Radiographic findings.*

Solitary cysts:	
air-filled	4
fluid-filled	2
Multiple cysts:	
air-filled	2
fluid-filled	4
Pneumothorax	3
Tumour-like	5

In 8 instances the cysts were localized to the right side and in 12 to the left. None was bilateral. In 19 cases the disease was unilobar and in one case multilobar.

Table 3 sets out the *radiological diagnosis*. In 12 cases radiography had shown cyst-like changes. Three patients had pneumothorax. In two of these, the correct diagnosis was not made until after supplementary tomography, after the lung had partially re-expanded, while in the third case the cysts were not demonstrable by radiography. Five of the cases had been diagnosed as tumours preoperatively. In one of these, tomography showed small, cystic translucencies interpreted as necrosis in a tumour. Three of these patients had homogeneous shadows, all of a juxta-hilar situation. At operation, all the cysts proved to have originated from the bronchial tree, and all contained pus.

In 6 cases radiography showed solitary and in another 6 multiple cysts. Six were filled with fluid and 6 with air.

It is apparent from what has been stated above, that in most cases the radiological diagnosis has not given rise to particular difficulties. Frequently, however, the plain films have to be supplemented with tomography or bronchography. Even so, the differential diagnosis from bronchiectasis may be extremely difficult, although the

localization may be suggestive. In bronchiectasis the basal segments of the lower lobe and the lingula are most frequently involved. Cysts, on the other hand, generally affect the upper lobe, although in our series there was a preponderance of lower-lobe involvement. The explanation is perhaps that the series contained 4 cases of so-called broncho-pulmonary sequestrations which are nearly always localized infero-posteriorly in the lower lobe.

Treatment

Table 4 lists the treatment in these 20 cases of lung cysts in infants and children. Six had segmental resection, 9 lobectomy, 1 pneumonectomy, and 3 enucleation. In one instance, operation was not believed to be indicated.

TABLE 4. *Operations.*

	No. of cases
Enucleation	3
Lobectomy	
right lower lobe	5
left upper lobe	1
left lower lobe	2
left upper lobe + lingula + + apical lower-lobe segment	1
Segmental resection	
right lower lobe	2
left upper lobe	3
left lower lobe	1
Pneumonectomy	1
Pleurotomy	1

Mortality and Postoperative Complications

Two patients died postoperatively. One of them was only one month of age and developed cardiac arrest immediately after the operation. The other patient was 4

months and succumbed to circulatory collapse on the day after the operation. Three patients had postoperative effusion, evacuated by thoracocentesis. One developed a bronchial fistula which closed spontaneously. Postoperative atelectasis or empyema did not occur.

Follow-up

Out of the 19 operated patients two died, as already mentioned, immediately after the operation. Of the remaining 17, two could not be traced. The follow-up period in the 15 cases ranges from 18 months to 12 years, average 5.3 years. Out of these 15 patients, 14 were entirely symptom free and their tolerance was up to that of other children of their own age. None had experienced pneumonic or asthmatic attacks after the operation, and none had clinically manifest pulmonary insufficiency. One patient was apt to become dyspnoeic when playing and tired easily.

Chest radiography did not in any case show signs of recurrent cysts. On the other hand, there were, as is usual following thoracotomy, more or less marked pleural changes in practically all cases. In the patient who was pneumonectomized at the age of 6 months, the heart had been

displaced to the extreme left, and the right lung occupied also the operated hemithorax.

Summary

A series of 20 infants and children with cysts of the lung is reported. Thirteen had a history of febrile pulmonary disease and one had had recurrent pneumothorax, whereas 6 had not presented any symptoms or signs until the last month before admission. The radiological findings are reviewed. It is concluded that it is impossible to decide, radiologically, clinically, or by histological examination, whether the cysts are acquired or congenital. Surgery consisted in pneumonectomy in one case, lobectomy in 9, segmental resection in 6, and enucleation in 3. In one case operation was not believed to be indicated. Recurrent infections, progressive enlargement of solitary cysts, or rupture of large or small subpleural cysts afford obvious indication for surgery. On the other hand, an expectant attitude is justifiable in cases of small cysts, detected by chance, which show no tendency to increase in size and no infection. All the operated patients included in the follow-up were symptom free except for one who was apt to become dyspnoeic on major exertions.

Kystes du poumon chez des enfants et des nourrissons.

L'auteur rapporte les observations qu'il a recueillies sur un groupe de 20 enfants et nourrissons atteints de kystes du poumon. Treize de ces sujets avaient souffert auparavant de maladies fébriles des poumons et un autre avait eu de multiples pneumothorax tandis que les 6 derniers n'avaient commencé à présenter des troubles ou des symptômes qu'à partir du dernier

mois ayant précédé leur entrée à l'hôpital. Les constatations radiologiques sont passées en revue. La conclusion que l'auteur en tire est qu'il est radiologiquement, cliniquement ou histologiquement impossible de déterminer si ces kystes ont été acquis ou sont d'origine congénitale. Le traitement chirurgical a consisté en une pneumectomie dans un cas, en une lobectomie dans 9 cas, en une résection partielle dans 6 cas et en une énucléation dans 3 cas. Dans le dernier cas, il fut estimé que l'intervention

chirurgicale n'était pas indiquée. Les infections récurrentes, l'augmentation progressive du volume de kystes solitaires ou l'éclatement de kystes sous-pleuraux de grandes ou de petites dimensions constituent autant d'indications formelles du traitement chirurgical. D'autre part une attitude d'expectative se justifie dans les cas de petits kystes décelés par hasard qui ne manifestent aucune tendance à augmenter de volume et ne s'accompagnent pas d'infection. Tous les patients opérés qui ont pu être suivis n'ont présenté aucune récurrence de leurs symptômes à l'exception d'un seul qui avait tendance à être affligé de dyspnée après un effort lourd.

Lungenzysten bei Kindern.

Es wird über eine Serie von 20 Klein- und anderen Kindern berichtet. Bei dreizehn lag eine Krankengeschichte von fieberhafter Lungenkrankung vor, eines hatte Rückfälle von Pneumothorax, während 6 keinerlei Symptome bis zum letzten Monat vor der Aufnahme ins Spital aufgewiesen hatten. Die röntgenologischen Befunde werden einer Übersicht unterzogen. Der Schluss wird gefolgert, dass es unmöglich sei es auf radiologischem, klinischem oder histologischem Wege zu entscheiden, ob die Zysten erworben oder angeboren seien. Die chirurgischen Eingriffe bestanden in Pneumotomie in einem Falle, Lobektomie bei 9, Segmentresektion bei 6 und Ausschälung bei 3 Fällen. Bei einem Falle war die Operation nicht angezeigt. Wiederkehrende Infektionen, fortschreitende Vergrößerung von Solitärzysten oder Ruptur grosser oder kleiner subpleuraler Zysten stellen offenbar eine Anzeige zur Opera-

tion dar. Dagegen ist eine abwartende Stellungnahme im Falle von kleinen, zufällig entdeckten Zysten, welche keine Tendenz zur Vergrößerung und Infektion zeigen, gerechtfertigt. Alle operierten Kranken wurden bei der Nachuntersuchung symptomfrei gefunden mit der Ausnahme eines Falles, der eine Neigung zur Atemlosigkeit bei grösserer Anstrengung aufwies.

Quistes del pulmón en infantes y niños.

Se presenta una serie de 20 infantes y niños con quistes del pulmón. Trece presentaban una historia pulmonar febril y uno había aquejado un neumotórax recurrente, mientras que seis no habían presentado ninguna manifestación hasta un mes antes de su ingreso. Se establece una revisión de los signos radiológicos. Se concluye que es imposible decidir radiológicamente, clínicamente o mediante el examen histológico si los quistes son congénitos o adquiridos. El acto quirúrgico consistió en la neumectomía en un caso, lobectomía en nueve, resección segmentaria en seis y enucleación en tres. En un caso se consideró que no se hallaba indicada la intervención. Constituyen indicaciones evidentes del tratamiento quirúrgico las infecciones recurrentes, la dilatación progresiva de quistes solitarios o la ruptura de quistes subpleurales, grandes o pequeños. Por otra parte, es lícito adoptar una actitud expectante en los casos de quistes pequeños expectantes casualmente, sin tendencia a aumentar de tamaño y sin manifestaciones infectivas. Todos los pacientes intervenidos sometidos a ulterior vigilancia permanecieron asintomáticos excepto uno que presentaba disnea de esfuerzo.

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Congenital Complete A-V Block in Three Siblings

by GÖRAN WALLGREN and ENRIQUE AGORIO

Complete A-V block is one of the very few diseases that can be diagnosed antenatally, through the presence of a continuously slow fetal heart rate. If the disease is diagnosed later in childhood, which is most often the case, some doubts, as to whether the disease is congenital or acquired may arise and certain requirements have to be fulfilled in order to rule out a postnatal etiology of the disease. These criteria were stated in 1929 by Yater (29), who considered a complete heart block to be congenital when diagnosed later in life only if a slow heart rate had been present early in life, together with symptoms of cardiac dysfunction, and if a previous heartafflicting disease could, with certainty, be ruled out.

Since the beginning of this century, when the first complete congenital heart-block was reported, approximately 100 cases of this disease in newborns have been published (21), a figure indicating, that this defect is a less common finding than most other cardiac anomalies of congenital origin.

There seems to be general agreement upon the fact that complete A-V block in childhood almost invariably is of congenital origin (8), but the opinions about the frequency of the disease as an isolated

defect, i.e. without associated cardiac malformation, vary a great deal. Yater 1933, Nielson 1935 and Steinberg *et al.* 1958 among others consider the combination with an associated heart lesion to be much more common than the isolated form, while others are of the contrary opinion. Keith *et al.* (8) reported that out of their 23 cases of complete congenital A-V block no less than 17 were isolated conduction defects, and Paul *et al.* (17) catheterizing 12 cases found associated heart lesions in only 5 of these. The discrepancy of opinions in this respect has very plausibly been explained by the fact that the auscultatory findings in most total A-V blocks, a harsh systolic ejection murmur over the left precordium, due to the increased stroke volume as well as the generally enlarged heart volume, may often have been misinterpreted as being due to an associated cardiac defect. It is generally agreed that, when an associated cardiac lesion is present, ventricular septal defects are the commonest ones. Wood (28) states that this lesion is found in approximately 10 % of all congenital A-V blocks and Donozo (5) reviewing 17 autopsied cases found this defect to be by far the most common associated lesion while only in 4 cases, was the conduction defect

found to be an isolated one. This latter statement does not contradict the opinion that isolated A-V blocks are a more common finding, but merely stresses the less favourable prognostic outlook in cases with an associated defect (13).

The anatomic and microscopic cause of the disease is to be found in the atrio-ventricular conduction system, and thorough microscopic investigations of this system have shown damage to, or complete absence of, the bundle of His (23, 24, 25, 26, 29, 30, 31). It is from an anatomical point of view interesting to note that hearts with complete absence of the inter-ventricular septum sometimes are found to have normal atrio-ventricular conduction.

Our knowledge about the etiological factors in this, as well as in other cardiac malformations is very incomplete, and the question of a hereditary component in these malformations, or of a temporary teratogenic factor is still open to much discussion.

The present article reports the occurrence of prenatally diagnosed complete A-V block in three births in one family, and is the first such report in the literature. It has been considered valuable to report this repeated malformation as additional evidence in the discussion of the etiology of the disease.

Case report

Both parents healthy. Born 1926.

First child born 1947. Male with a birth-weight of 3450 g. Gestation complicated by a slightly elevated blood pressure and albuminuria. Slow fetal puls rate (50/min) noted in mens 8 and at successive examinations. Frontal head first delivery. Umbilical cord

twice around the neck. Small placental infarction, otherwise normal. Immediately postnatally the child was in very good condition. ECG showed the presence of a complete A-V block with a ventricular rate maintained at approximately 40/min. The atrial rate was around 130/min. QRS-complex of normal shape. The electrical axis showed a normal right deviation. On the second day of life the condition of the child deteriorated somewhat and showed signs of peripheral cyanosis. The heart rate was 38/min and a systolic murmur was heard over the entire precordium. This murmur had already been auscultated at birth, but was now somewhat louder. No signs of right sided failure were noted. During the next few days his condition deteriorated further with constant cyanosis and prolonged attacks of apnea. The heart rate was at all times around 35/min. The child expired on the 4th day of life with central circulatory insufficiency. Post-mortem examination revealed hyperemic organs with small bronchopneumonic areas in the basal parts of the lungs with associated atelectatic areas. The myocardium was hyperemic and somewhat edematous with splitting up of the muscular fibrils. There were no signs of a myocardial inflammatory reaction. There was a barely patent ductus arteriosus.

Second child born 1952. Male with a birth-weight of 4110 g. Uncomplicated gestation. Fetal heart rate of less than 70 was noted 2 months ante partem. Uneventful delivery. The child immediately postnatally was in good condition. ECG showed the presence of a complete A-V block with a ventricular rate of 45/min. and an atrial rate of 150/min. QRS-complexes were normal. P-waves were somewhat pinched. Right-sided deviation of the electrical axis. Chest x-ray examination showed a generally enlarged heart (100 ml). Atelectatic areas were found in the left lung. On fluoroscopy there was a marked atrioventricular contraction dissociation. On auscultation there was a short, harsh systolic murmur maximum over the third left intercostal space. No signs of

right ventricular insufficiency. The child during the first days was in relatively good condition, but became cyanotic at feeding-time. Pulserate was maintained at 45/min. On the seventh day of life peripheral edema was noted and the general condition of the child had now deteriorated with more pronounced respiratory distress and signs of stasis. Pulserate and auscultation as before. The child expired on its 10th day of life in a state of central circulatory insufficiency with organo-stasis. Post-mortem examination revealed generalized stasis and minimal bronchopneumonia. The myocardium showed no signs of inflammatory reaction. A generalized myocardial hypertrophy was present. There was a barely patent ductus arteriosus, and a patent foramen ovale.

Third child spontaneous abortion in mens V 1956. No anatomical examination.

The gestation up to the abortion was reported uneventful. As we have no clinical or anatomical data in this case we have no means of appreciating the condition of the heart.

Fourth child born 1958. Male with a birth-weight of 4770 g. Uncomplicated gestation. Slow fetal heart rate observed at auscultation some weeks before delivery. Because of the previous difficulties and the suspicion of a conduction defect, this pregnancy was terminated at full term by forceps delivery. The child at delivery was in good condition. Heart rate was approximately 70/min. ECG showed the presence of a complete A-V block with a ventricular rate of 75/min and an atrial rate of 105/min. QRS-complexes were normal. P-waves pinched. Right sided electrical axis. On auscultation no pathological murmurs were heard. X-ray examination showed a generally enlarged heart with an absolute volume of 87 ml. No signs of parenchymal infiltrations in the lungs. The child during the stay in Hospital was in very good condition. The pulserate was kept spontaneously at 67-75/min. The child was dismissed from the Hospital in the third week of life, and has at subsequent observations

at the age of 2 and 5 months been found to be in excellent condition with a pulserate of approximately 70.

Discussion

It is generally accepted that the isolated complete A-V blocks of congenital origin have a good prognosis (3, 5) and these patients have been reported to live to old age without disabling symptoms (3). The high and early mortality in the presently reported cases of isolated complete A-V block indicates that there seems to be a dangerous period immediately after birth, and that already at this time, there is a sorting out of the functionally less capable hearts, which are unable to survive beyond the neonatal period. It is, quite naturally, primarily the spontaneous ability of keeping an adequate heart rate that seems to be the essential factor for determining the viability of the newborn. The present cases show a distinct difference in this respect, with a ventricular rate in the two not surviving newborns of 45/min or less, while the surviving case kept a spontaneous rhythm of not less than 65/min. In spite of the compensatory increase in stroke volume of the heart, a satisfactory minute volume, compatible with life, can evidently not be maintained with the lower pulse rate. The effect of this discrepancy is a "forward failure" of the heart, eventually terminating the life of the patient. As the effective stroke-volume of the heart can only increase to a certain extent, the regulatory factor remains ultimately the spontaneous ventricular rate, which unfortunately in many cases remains more or less unaffected by the administration of drugs. We are thus

left without good therapeutic means by which we might interfere with the often fatal outcome of the disease.

The familial occurrence of conduction disturbances has previously been reported in the literature. Morquio in 1901 (12) reported 5 brothers with clinical signs of impaired atrio-ventricular conduction, and Sir William Osler in 1903 described a family in which most of the members had a slow pulse rate and Stokes Adams syncope. Fulton (6), Canabal *et al.* (4) and Stephan (20) have, among others, reported the familial occurrence of different degree of A-V block in 2 or more members of a family. However, in none of these cases have the criteria of Yater for the diagnosis of a congenital defect been fulfilled. Aylward in 1928 (2) reported the first two cases of complete A-V block in two sisters, which, as confirmed later by Aitken (1), both fulfilled the criteria advanced by Yater. In 1938 Wallgren & Winblad (24) reported a family where two of five children had cardiac malformations, accepted as congenital, one of which was diagnosed as a complete A-V block, and where different varieties of cardiac defects, including conduction disturbances were found in the father as well as in other members of the family. A similar case report is given by Wendkos & Study (25) who also find conduction defects in parents of children with congenital A-V block. The fact that in many of these cases the conduction defect has been found in more than one generation has naturally aroused the suspicion that a genetically bound factor may have been present. The familial occurrence of other cardiac malformations is well known, and McKeown *et al.* (11) state that the chances for other offsprings

in a family where cardiopathy is already present in one child, to be born with a cardiac malformation is 1.8% while the corresponding figure in a normal population is less than 0.5%. Lamy & Schweisguth (9) and Polani & Campbell (19) have both by means of large series studied the frequency of repeated cardiac malformations in families where one already exists and have come to similar conclusions. They have been impressed by the higher frequency in these families and have discussed the possibility of a recessive hereditary pathway.

In the present case it was possible to obtain a pedigree from more than three generations back, and information about more than 75 people in the family tree was collected, including 29 first cousins of the actual cases. No signs of congenital disease were reported in any of them. This negative finding naturally does not completely exclude the possibility of a recessive hereditary factor, but the chances for all three children to be affected with the anomaly would be in the order of 1:64. This mode of transmission consequently is not readily acceptable and instead, a suddenly induced teratogenic factor should be looked for.

It is well known that embryopathy may be induced, either by influence upon the embryo itself, or upon the maternal and paternal genes, or through influence on both of these ways (14).

Apart from maternal viruses and maternal age, which could be excluded as predisposing moments in the present case, factors influencing the embryogenesis itself are known to be numerous. Experimental work has been done proving the teratogenic effect of, among other agents, hy-

poxia, hypoglycemia, avitaminosis, irradiation and the use of antimetabolites in the mother. Through the pioneer work of Stockard in 1921, a time-specificity was found to exist for the induced malformations, i.e., induced at different stages of gestation, the teratogenic agent would give rise to different forms of malformations. It has also recently been suggested (27) that there exists an agent-specificity, i.e., different agents would be capable of inducing different forms of malformations. If an environmental factor, such as described above, should be held responsible for the malformations in the actual cases, it must be assumed, that a teratogenic agent would have influenced the fetal organogenesis at a specific time (approximately the 5th week of gestation), and that this environmental influence would be repeated at the critical time in all three gestations. This indeed would be too co-incidental to allow acceptance of this mechanism.

The teratogenic effect brought about by specific tissue immunization, as demonstrated by Gluecksohn-Waelsch (1954), may also be considered as a plausible etiological cause of the present malformations. The theoretical background for such a mechanism precludes that a spontaneous immunization would have occurred, with the production of antibodies directed against a specific protein of the conduction system of the fetal heart. The study of such a mechanism would be based upon the detection of such specific antibodies, which in turn would require the use of a medium containing proteins from the bundle of His in the actual child, and as such is not possible. The routine study of the serological conditions in the mother and child did not reveal any abnormalities,

which however has no bearing upon the presence or absence of a specific tissue immunization. The fact that the abnormality occurred in the first child would speak against the immunization mechanism, but it is difficult to say whether it rules it out completely.

The sudden appearance of a repeated congenital malformation in a family, where previously no teratogenic manifestations were seen, speaks more in favour of an induced disturbance in the maternal or paternal genetic pattern.

The genetic status of healthy parents may drastically be influenced by mutations, with the potential danger of a consequent phenotypic manifestation in the offsprings. Such mutations are known to occur spontaneously by failure of the gene to duplicate at the time of cell division, by irradiation from natural sources, or by the action of chemical mutagenic factors during the lifetime of the parents (18). Also the withdrawal of a suppressor gene, which, if present, would prohibit the appearance of a phenotypic manifestation, has been suggested as an explanation of sudden, unexpected interference with the normal embryonic development (10). Any of these changes in the genetic pattern may have been responsible in the actual cases, and are indeed likely to have occurred, as the presence of repeated identical malformations in the offsprings suggests a genetically bound transmittance of the disease, rather than an environmental factor influencing the embryogenesis itself.

It is of some interest to note that the presently reported siblings were all of the same sex. Reviewing the literature it is clear that this has also been the case in

most of the reported familial occurrences of congenital complete A-V block (1, 4, 12, 25). As this phenomenon seems to be an almost constant finding it is difficult to dismiss it as being purely co-incidental, and it may be questioned whether the teratogenic factor is linked to any of the sex chromosomes.

It is well known, that from a genetic point of view, the human malformations present a very complex problem indeed, and our knowledge about the different behaviour of the genes themselves is certainly, not by far, enough to allow us to understand anything, but some simple hereditary pathways. For the rest, we can so far only speculate and hope that the great amount of research that is being done in this field eventually will help in understanding and thus preventing a

group of diseases, that today represent one of the leading causes of neonatal deaths.

Summary

A case report i given of three siblings in one family, all with isolated complete A-V block diagnosed antenatally. Two of the siblings expired less than 10 days old. Both of them had a spontaneous pulse rate of 45 or less. The third child survived and had a ventricular rate of 65 or more. The relevant literature is reviewed and prognostic and etiological factors are discussed. The authors arrive to the conclusion, that the teratogenic effect might be due to an induced mutation in the parental genes, resulting in phenotypic manifestations in the offsprings.

Dissociation auriculo-ventriculaire complète congénitale.

Trois enfants, frères et sœur, présentaient à la naissance une dissociation auriculo-ventriculaire complète. Deux d'entre eux sont morts avant le dixième jour : leur fréquence cardiaque était égale ou inférieure à 45 par minute. Le troisième enfant a survécu : sa fréquence cardiaque atteint, au moins 65 battements par minute. Une revue de la littérature a été faite; les facteurs étiologiques et le pronostic de l'affection sont discutés. Les auteurs concluent que le facteur tératogène pourrait être trouvé dans une mutation au niveau des gènes des parents; les résultats de cette mutation s'expriment par des manifestations phénotypiques chez leurs descendants.

Isolierter kompletter A-V Block bei drei Geschwistern.

Es wird von drei Geschwistern einer Familie berichtet, bei denen praenatal ein isolierter kompletter A-V Block diagnostiziert wurde.

Zwei der Kindern starben innerhalb der ersten 10 Lebenstage. Beide hatten einen spontanen Puls von 45 oder weniger. Das dritte Kind überlebte und hatte einen spontanen Puls von 65 oder mehr. Die betreffende Literatur wird berücksichtigt und prognostische und aetiologische Faktoren werden diskutiert. Die Autoren kommen zu dem Schluss, dass der teratogene Effekt durch eine induzierte Mutation in den elterlichen Genen bedingt sein könnte, die in der phänotypischen Manifestation der Nachkommen resultiert.

Tres casos familiares de bloqueo auriculo-ventricular completo.

Tres casos de bloqueo auriculo-ventricular completo sin otra malformación asociada, son estudiados en tres hermanos. En los tres casos el diagnóstico fué prenatal. Dos de los hermanos fallecieron antes de los 10 días de vida, ambos presentaban un pulso de 45 o menos. El tercer paciente sobrevivió presentando una frecuencia ventricular de 65 o más. Es revisada la literatura

concerniente y los factores pronósticos y etiológicos son discutidos. Los autores llegan a la conclusión que el efecto teratogénico podría ser

debido a una mutación inducida en los genes de los padres, dando como resultado manifestaciones fenotípicas en los hijos.

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Kidney Lesions Associated with Anaphylactoid Purpura in Children

by A. BERGSTRAND, C. G. BERGSTRAND and H. BUCHT

It is well recognized that anaphylactoid purpura (Schönlein-Henoch syndrome) often is accompanied by renal symptoms. According to several reports in the literature (4, 5, 15, 16, 24) about 50 per cent of all children with anaphylactoid purpura have proteinuria and haematuria of varying degree during some stage of the disease. In other series a much lower incidence of renal complications has been found (14, 18, 20). There seem to be few clinical features which really distinguish this renal disorder from the classical glomerulonephritis. Certain differences have, however, been pointed out. The haematuria which may accompany the Schönlein-Henoch syndrome is regarded as more persistent, the erythrocyte sedimentation rate, according to Derham & Rogerson, tends to become normal within a short time despite continued haematuria, hypertension is not commonly found and nitrogen retention is rare. It has even been suggested (5) that the initial renal involvement is indeed better described as "renal bleeding" than as a true nephritis. Histological studies

and the fact that some cases develop chronic renal insufficiency hardly support such a conception.

The histological investigations of this disease (5, 7, 10, 12, 19) have been made on autopsy material from patients with severe symptoms, who died in renal failure. The purpose of the present work was to study the kidney lesions in biopsy specimens from patients in relatively early stages of the disease with less pronounced clinical signs of renal involvement and without renal failure. It was thought that such a study would give a more accurate picture of the renal lesions and a better understanding of the nature of the disorder, as well as some information on prognosis, which is regarded as poor by many authors. A similar investigation has recently been published by Vernier et al.

Material and Methods

The method of renal biopsy was essentially the same as used in adults and described by Kark & Muerhcke. The application of the method in children and the technical details have been discussed by Bergstrand & Bucht (2). Biopsy was performed with the patient in the prone position and in local anaesthesia.

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TABLE 1. *Clinical data at the time of biopsy.*

Case no.	Name	Sex	Age in years	Duration of haematuria	Blood pressure	Protein-uria	Haemat-uria	NPN mg per 100 ml plasma	Actual value	Endogenous creatinine clearance ml per min	Urinary concen- tration capax- ty (spec. grav.)
										per 1.73 sq. m body surface ³	
1	G.B.	M	10	10 months	125/75	+	+++	42	51	79 ⁴	1.025
2	Y.E.	F	13 ¹	3 y. 4 m.	105/65	+	++	25	61	82	1.032
			15 ²	5 y. 1 m.	120/55	+	++	26	75	94	1.027
3	L.W.	M	7 ¹	11 months	125/75	traces	++	38	49	98	1.032
			9 ²	2 y. 8 m.	95/65	traces	++	26	34	64	1.029
4	B.S.	F	9	4 months	125/75	traces	++	25	30 ²	55	1.029
5	U.W.	F	14 1/2	—	90/55	traces	0	26	88	97	1.026
6	Y.A.	F	12	2 y. 4 m.	110/75	traces	+	30	75	94	1.029

¹ First biopsy. ² Second biopsy. ³ Normal values 100 ml per min \pm 15 %.⁴ Later values normal.

The biopsy material was immediately fixed in 10 per cent formol solution. From the paraffin blocks sections were cut with a thickness of one to three micron. They were stained with haematoxylin-eosin, with Lade- wig's modification of Mallory's staining and with Weigert's staining for elastic tissue.

Renal function was measured by endoge- nous creatinine clearance test and by ordi- nary water load and concentration tests. In Case 1 inulin and paraaminohippuric acid clearances were also determined. In all the cases platelets counts, bleeding time and coagulation time were made and the results were normal.

Six patients were studied. Clinical data at the time of biopsy are presented in Table 1.

Case Reports

CASE 1. G.B. (K.L.B. 88/57) was a boy, 10 years old when first admitted to the Hospital in January 1957. His present illness had started 9 months before with the develop- ment of petechial bleedings and macules of varying size which gradually faded and be- came light brown. The skin lesions had pos- sibly followed an infection with german measles. This could, however, not be defini-

tely established. A few days later he had blood in the stools, abdominal pain and dark coloured urine. He developed generalized oedema and was referred to hospital. He had then large amounts of protein in the urine, microscopic haematuria and casts. His serum protein value was 3.5 per cent and paper electrophoresis revealed a protein pat- tern typical of a nephrotic syndrome. Serum cholesterol was 405 mg per 100 ml. Erythro- cyte sedimentation rate was high, 37-50 mm per hour. Blood pressure, non protein nitro- gen and renal function tests were normal. The antistreptolysin titer was also normal.

The oedema vanished and did not recur during the three years the patient was ob- served. No relapse of the skin lesions oc- curred. Throughout the time of observation the patient had proteinuria and haematuria of varying degree, hypoalbuminaemia, ele- vated erythrocyte sedimentation rate and during the first two years increased serum cholesterol. Blood pressure, antistreptolysin titer and renal function tests (including paraaminohippuric acid clearance and inulin clearance) remained normal.

Renal biopsy was made in February 1957 ten months after his renal disease had started.

Microscopic examination. In several glomeruli the basement membrane of Bowman's capsule was definitely thickened. The glomerular capillaries were collapsed with a focal thickening of the basement membrane and occasional adhesions to Bowman's capsule. There was also an increased number of cells in several of the glomerular tufts which were divided into smaller separate units (segmentation). In one glomerulus a large hyaline mass with a number of cell nuclei was observed, which connected several capillary loops with Bowman's capsule. This may be a remnant of an epithelial proliferation from the cells of Bowman's capsule (crescent) as seen in subacute haemorrhagic glomerulonephritis. There were, however, no definite crescents and no other signs of acute or subacute glomerulonephritis. Many glomeruli showed no pathological changes. There were no changes in the arterioles. The proximal tubules were slightly dilated but there were no changes in the epithelial cells as observed in association with a nephrotic syndrome. There were several small areas in the interstitial tissue with an increased amount of connective tissue and a small number of lymphocytes.

CASE 2. Y.E. (K.L.B. 119/54) was a 10-years-old girl when first admitted to the Hospital in 1954. Her present illness had started in 1948. She had then been in another hospital with a diagnosis of anaphylactoid purpura and abdominal colic. Every year since then she had been ill several times with the same type of skin lesion, swollen joints and abdominal pain. Blood had been observed in the stools at least once. The urine had not been examined during this period. She had scarlet fever in 1953 without complications.

Proteinuria was first observed late in 1953 about two months before her first admission. She had a microscopic haematuria but no casts. Blood pressure, non-protein nitrogen and erythrocyte sedimentation rate were normal. A throat culture revealed beta-haemolytic streptococci but the antistreptolysin titer was not increased.

During the following period of observation (1954-1959) the patient was admitted to the Hospital several times. Except for a short time in 1956, she had persisting proteinuria and haematuria of varying degree with a severe exacerbation about one year after her first admission. She then had gross haematuria, severe proteinuria, nitrogen retention and high erythrocyte sedimentation rate but normal blood pressure. In association with this the patient had an attack of purpura. Throughout the period of observation the patient had normal renal function tests, normal antistreptolysin titer and a normal serum protein pattern. With the exception of the exacerbation mentioned above, the erythrocyte sedimentation rate was normal.

Since late spring in 1957, more than three years after her first admission, the proteinuria and haematuria showed a tendency to decrease but when the patient was last seen in January 1959 she still had small amounts of protein in the urine and microscopic haematuria.

Renal biopsy was first made in April 1957 a little more than three years after the renal symptoms were detected. A second biopsy was made in January 1959.

Microscopic examination. First biopsy (April, 1957). In one glomerulus a large segment of the capillary tuft was destroyed and converted into a hyaline mass containing a number of cell nuclei (Fig. 1). This area was completely adherent to Bowman's capsule. In other glomeruli there was a focal thickening of the capillary basement membrane and adhesions between the capillaries and Bowman's capsule (Fig. 2). The glomerular lesions were thus similar to those seen in Case 1 but there was no thickening of the basement membrane of Bowman's capsule. There were several glomeruli without any lesions. No changes could be observed in the arterioles, tubules or interstitial tissue.

Second biopsy (January, 1959). Similar changes as described above were observed. There were no signs that the lesion was progressing.

CASE 3. L.W. (K.L.B. 536/56) was a boy,

7 years old when first admitted in 1956 to the Hospital. About a fortnight before he had complained of joint pains and about the same time petechial bleeding was observed. On the day of admission he had abdominal pain, vomiting and blood in the stools. The urine contained small amounts of protein and haematuria was present. No casts were observed. Blood pressure and non-protein nitrogen were normal. Erythrocyte sedimentation rate was slightly elevated. Beta-haemolytic streptococci were cultured in very small numbers from the throat. The antistreptolysin titer was insignificantly increased.

Throughout the following period of observation (1956-1959) the patient had proteinuria and haematuria of varying degree, occasionally with severe exacerbations; however, non-protein nitrogen and blood pressure remained normal. The erythrocyte sedimentation rate was moderately increased during the first year but later became normal. Throat cultures were repeatedly negative for beta-haemolytic streptococci. The antistreptolysin titer was normal with the exception of a few months in 1957 when increased values were demonstrated. Serum protein pattern and renal function tests were essentially normal.

Renal biopsy was first made in April 1957 one year after the patient's nephritis had started. A second biopsy was made in January 1959.

Microscopic examination. First biopsy (April, 1957). One glomerulus was completely destroyed and converted into a hyaline scar (Fig. 3). No corresponding vascular changes were observed. In several glomeruli moderate changes similar to those observed in Case 1 and 2 were demonstrated. There were also some glomeruli with very slight changes or no lesions at all.

Second biopsy (January, 1959). One completely destroyed glomerulus was observed also in this specimen and there were several glomeruli with changes similar to those already described. There were no signs that the disease was progressing.

CASE 4. B.S. (K.L.B. 1194/56) was a girl, 8 years old when first admitted to the

Hospital in November 1956. Two years before she had been ill for three weeks with fever and a sore throat. Streptococci had been demonstrated by culture, but no rash was observed. There had been proteinuria for a fortnight. Her present illness started about six weeks before her admission with purpura, abdominal pain, vomiting, swollen and painful joints and facial oedema. She had fever about a fortnight. The stools were normal. Proteinuria was first observed three weeks later. On admission she had a slight proteinuria, gross haematuria but no casts and a normal non-protein nitrogen value. Her blood pressure was slightly increased (145/75 mm) but became normal within a few days. The erythrocyte sedimentation rate was slightly to moderately increased. Beta-haemolytic streptococci could not be isolated from the throat. The antistreptolysin titer was normal. The serum protein pattern was normal.

During the first months of the observation period (1956-1959) the patient had a slight proteinuria, which finally disappeared. Haematuria of a moderate degree was present for about eight months. The urine then remained normal and an Addis count in April 1958, seventeen months after her illness had started, gave a normal value. Renal function tests revealed nothing abnormal.

Renal biopsy was made in February 1957, four months after proteinuria was first observed.

Microscopic examination. In several glomeruli there were moderate changes of the same appearance as described in the other cases. There were also several undamaged glomeruli. No changes were observed in other parts of the nephrons, the minute vessels or the interstitial connective tissue.

CASE 5. U.W. (K.L.B. 80/59) was a girl, 14 years old when admitted to the Hospital in January 1959. After parotitis in 1948 she had had a typical attack of anaphylactoid purpura and in the following year macules had been observed on the legs and arms at several occasions. Otherwise she had been healthy. At a routine examination in 1958 a

slight proteinuria was discovered and the patient was referred to the Hospital. Microscopic examination of the urine, including an Addis count, was normal. Blood pressure, non-protein nitrogen and renal function tests were also normal. In a few urinary specimens traces of protein were found.

Renal biopsy was made in January 1959.

Microscopic examination. The histological examination did not reveal any changes.

CASE 6. Y.A. (K.L.B. 111/59) was a 3-years-old girl when she was first admitted to the Hospital in 1950. She had had subfebrile temperature and swollen painful joints. On admission she had petechial and macular bleedings in the skin and a diagnosis of anaphylactoid purpura was made. Her urine was normal. The erythrocyte sedimentation rate was slightly elevated. The antistreptolysin titer was normal. Six years later (1956) the patient was admitted to the surgical department with acute abdominal pains. She had a microscopic haematuria, increased erythrocyte sedimentation rate and a slightly elevated blood pressure.

During the following period of observation (1956-1959) the patient had proteinuria only on a few occasions but a persistent microscopic haematuria with abnormal Addis counts. The erythrocyte sedimentation rate was normal or slightly increased.

When the patient was seen in January 1959 the Addis count was still abnormal but no proteinuria was demonstrated and renal function tests were normal. The antistreptolysin titer had not been regularly followed in this patient. It had been increased in 1956 and 1957 on two occasions.

Renal biopsy was made in February 1959.

Microscopic examination. No changes were observed in this specimen.

Discussion

The anaphylactoid purpura is, as suggested by the name, usually considered an allergic disorder. There is good evidence

that anaphylactoid purpura belongs to a group of diseases, including acute nephritis, rheumatic fever and polyarteritis nodosa, in which an antigen-antibody reaction is an important pathogenetic factor (7, 9, 11). The vascular lesions seen in the skin in anaphylactoid purpura resemble those observed in other allergic disorders. In severe cases they may develop into a necrotizing arteriolitis, which is occasionally localized also to organs other than the skin.

It could be expected that the renal lesions associated with anaphylactoid purpura should resemble those found in haemorrhagic glomerulonephritis. This may be the case, judging from the studies made on autopsy material. The renal pathology has been described as glomerulonephritis, nephritis Type I according to Ellis, mixed Ellis Type I and II nephritis, subacute nephritis, tubular nephrosis and chronic nephritis. These diagnoses cover a wide range of renal lesions more or less corresponding to different clinical pictures which are seen in different stages of haemorrhagic glomerulonephritis. There seems to be little doubt that the kidney disease of anaphylactoid purpura may develop along the same lines as haemorrhagic glomerulonephritis and that the pathology of the final stages is essentially the same.

In the present study glomerular lesions were observed in four of the patients. These changes were practically identical and there were only minor degrees of difference among the four cases. In Cases 1, 2 and 3 one or more glomeruli were severely damaged and most of the other glomeruli showed slight or moderate lesions. In Case 4 the changes were less pronounced but quite evident.

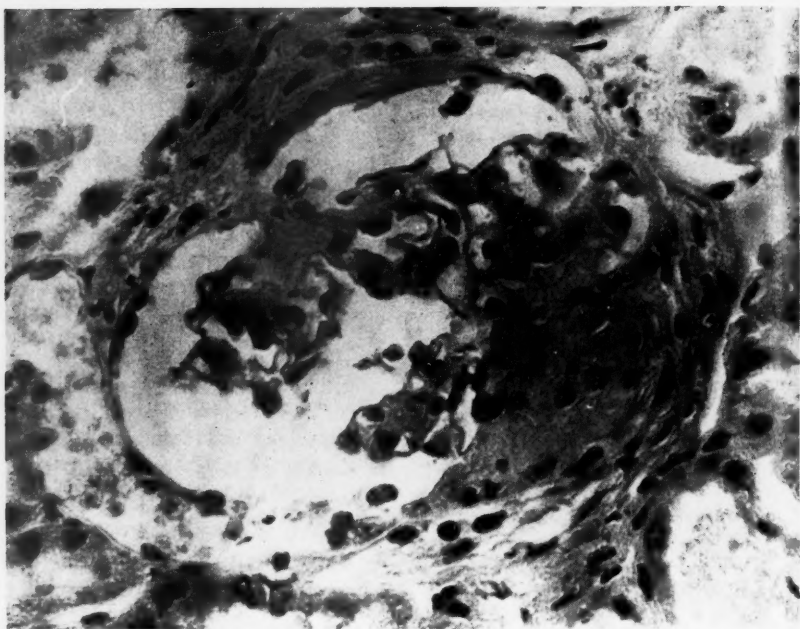


Fig. 1. Case 2. Severe lesion. Partly destroyed glomerulus with a crescent-like adhesion between the capillary loops and Bowman's capsule. The capillary walls are converted into a hyaline mass containing a large number of remaining cell nuclei. Htx-Eosin. 175 \times .

In a previous study of renal biopsy specimens from healthy voluntary humans, aged 20–25 years, occasional glomerular changes have been observed, comparable to those described here as slight or moderate (1). It has not been possible to perform such an investigation in children. Thus, it cannot be excluded that similar mild glomerular changes are also present in clinically healthy children. However, the more severe changes observed in the present patients are probably signs of a disease, which has seriously involved and partly destroyed a number of glomeruli. It is therefore most probable that the slight and moderate changes are sequelae of the same disease, especially as

they are not observed occasionally but in a large number of glomeruli.

In allergic diseases the renal vascular changes are usually found in the interlobular arteries and larger vessels. Vessels of this size were not present in the specimens examined. In the glomerular capillaries fibrinoid necrosis and fibrin thrombi are usually considered as signs of an allergic reaction. No such changes were found in the present material. This does not exclude an allergic reaction as a pathogenetic factor.

In none of the specimens examined were erythrocytes observed in the glomerular capsules or in the tubular lumina. No haemorrhage could any bleeding be demonstrated in

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Fig. 2. Case 2. Moderate lesion. Partly collapsed glomerular capillary loops with a focal hyaline thickening of the walls and adhesions to Bowman's capsule. The central wide lumen is probably part of the capsular space, which has been isolated through adhesions between the capillary loops. Htx-Eosin. 175 \times .

the interstitial tissue. Thus the observations do not sustain the opinion that the haematuria is only "a renal bleeding".

The fact that no changes in the arterioles were demonstrated in the kidneys in the present investigation indicates that the lesions observed must be regarded as remnants of an inflammatory process, a glomerulonephritis. Absence of morphological signs of an active inflammatory reaction does not exclude such a conception.

Our knowledge of the anatomical lesions in acute or subacute haemorrhagic glomerulonephritis is mainly based on studies of autopsy material from patients who

had severe symptoms and died from the disease in these stages. The changes seen in the acute phase of haemorrhagic glomerulonephritis have also been studied in biopsy specimens by Brun *et al.* and by Vernier *et al.* From a clinical point of view none of these cases are quite comparable to the renal disease associated with anaphylactoid purpura as illustrated by the present patients. A very few glomeruli (Case 1 and 2) certainly showed changes which could be interpreted as hyalinized crescents similar to those seen in subacute haemorrhagic glomerulonephritis but these observations hardly allow definite conclusions.

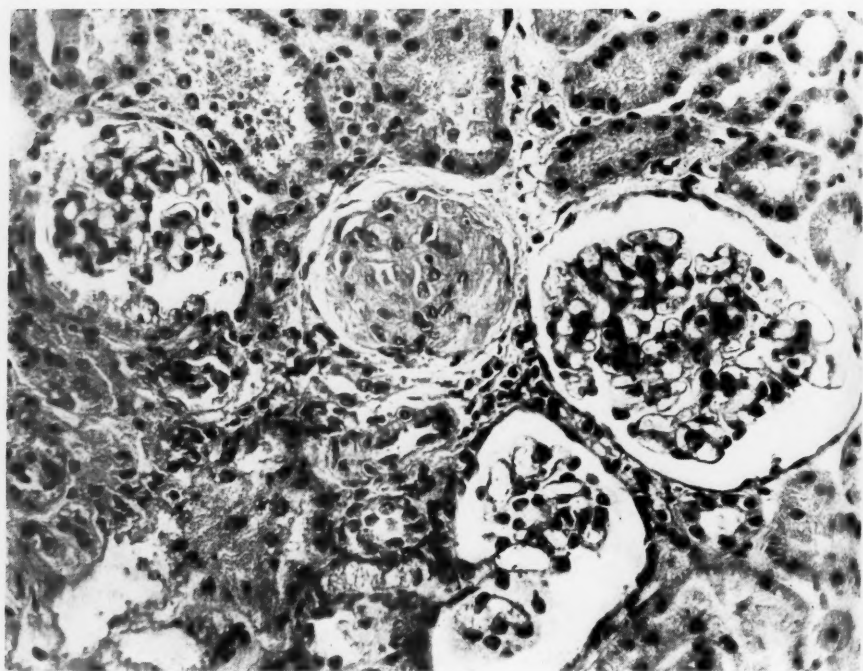


Fig. 3. Case 3. Severe lesion. The central glomerulus is completely destroyed and converted into a hyaline scar. The other glomeruli are intact. Htx-Eosin. 125 \times .

The association of anaphylactoid purpura and the nephrotic syndrome is interesting. There are several reports of such cases (5, 6, 7, 13, 15, 17) where hypoproteinaemia, hyperlipaemia and massive proteinuria developed during the course of the disease. Whether the renal disease of anaphylactoid purpura really has a more marked tendency to develop nephrotic symptoms than other types of nephritis seen in children seems, however, impossible to decide from available reports.

The glomerular lesions of "lipoid nephrosis" and chronic parenchymatous glomerulonephritis (Ellis Type II) are rather well known since patients with these dis-

eases often died before the "antibiotic era" from intercurrent infections before renal failure had developed. Biopsy material has also been studied (22). There are, no doubt, similarities also between the glomerular lesions described in the present paper and those associated with the nephrotic syndrome. This is, as could be expected, more marked in the patient G.B. (Case 1) who developed nephrotic symptoms in the beginning of his disease, but it is quite evident also in the other patients. However, the tubular changes associated with the nephrotic syndrome could not be demonstrated in any of the patients. Thus the renal changes of ana-

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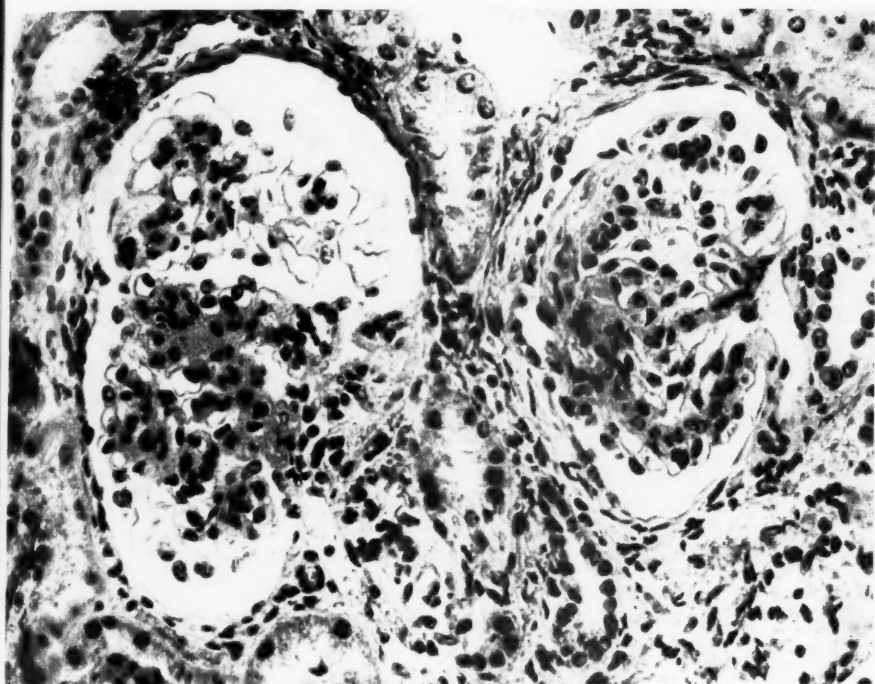


Fig. 4. Case 3. Slight changes. Two glomeruli with focal thickening of the capillary walls, segmentation of the glomerular tuft and small adhesions to Bowman's capsule. Ladevig stain. 150 \times .

phyllactoid purpura as observed in the present material cannot be regarded as identical with those of "lipoid nephrosis" or other diseases with a nephrotic picture.

How the glomerular changes described should best be classified is more or less a question of academic interest and cannot be solved without further investigations of the pathology of the renal diseases in children. At present it seems only possible to state that in anaphylactoid purpura there may occur definite glomerular lesions, probably sequelae to a glomerulonephritis and associated with the clinical picture of persistent haematuria without signs of renal insufficiency.

Vernier *et al.* (23) found glomerular changes in their patients with anaphylactoid purpura very similar to those described here. They consider the renal involvement as "not related closely to the renal lesion of acute glomerulonephritis". Their studies indicated that the changes more resemble those seen in disseminated lupus erythematosus.

The question whether the changes described in this paper are typical of the renal disorder associated with anaphylactoid purpura seems impossible to answer with certainty since there are very few investigations in children with other renal disease studied by renal biopsy.

In rare, rapidly fatal cases of thrombocytopenic purpura necrotizing arteriolitis with fibrin thrombi and fibrinoid necrosis are observed inter al. in the skin in connection with purpuric spots or a rash. Renal lesions with rapid renal failure may occur. In the glomeruli fibrin thrombi and fibrinoid necroses are seen in the capillaries (21). This disease, which is called "Moschcowitz syndrome" has thus some features in common with anaphylactoid purpura. Its close relationship to the generalized Schwarzmans reaction has been pointed out by many authors.

It could therefore be presumed that the renal lesions in anaphylactoid purpura are of the same nature as those of "Moschcowitz syndrome". Both are probably allergic reactions, the latter acute and fatal, the former much less severe with signs of healing. The fact that an inflammatory reaction with an exudate rich in polymorpho-nuclear leucocytes and epithelial proliferation (crescents) is almost completely absent in both types of purpura in contrast to the common haemorrhagic glomerulonephritis may be in favour of this conception. This does, of course, not imply that these two types of purpura should be regarded as different stages of the same disease.

Most authors feel that the prognosis of the renal disease associated with anaphylactoid purpura is serious. Derham & Rogerson, using Addis counts and urea clearance tests as criteria, found an incidence of chronic nephritis of not less than 6 per cent in their series. It has, on the other hand, repeatedly been pointed out that kidney function, as measured by clearance tests, may be entirely normal in spite of proteinuria and haematuria

persisting for many years and that the urinary abnormalities ultimately may subside.

Judging from the histologic examination of the biopsy specimens there are little or no signs of an active renal disease in the patients presented here. Furthermore, in the two cases where a second biopsy was made, more than one and a half year after the first one, no signs of progress of the disease could be observed. Even if the difficulties to interpret and classify the renal changes are taken into consideration it seems justified to state that the histological observations are in favour of a good prognosis in the patients of the present study.

Summary

1. Six children, 7 to 15 years old, with anaphylactoid purpura and signs of renal involvement were examined. The clinical findings and the results of histological studies made on specimens obtained by renal biopsy are described.

2. Relevant clinical data at the time of biopsy are presented in Table 1. All patients had proteinuria and five of them had a more or less marked haematuria. None of them showed definite clinical signs of renal insufficiency.

3. In four of the patients with longstanding haematuria glomerular lesions were found. These changes are regarded as remnants of an inflammatory process and their classification is discussed.

4. In two patients a second biopsy was performed after an interval of almost 2 years. No progress of the histological lesions was demonstrated.

5. The histological studies seem to support the conception that the prognosis of

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the kidney disorder associated with anaphylactoid purpura may not be unfavourable even in cases with persistent haematuria.

Addendum

After this paper was submitted for publication another case has been studied. The

patient, a 4-years-old boy, had had haematuria only for 4 weeks when the biopsy was made. The histological examination revealed rather pronounced changes of the same type as observed in the other patients.

Lésions rénales accompagnant un purpura anaphylactoïde chez des enfants

Six enfants âgés de 7 à 15 ans et présentant un purpura anaphylactoïde ainsi que des signes de lésions rénales ont été examinés. Les auteurs rapportent les constatations cliniques qu'ils ont recueillies ainsi que les résultats des examens histologiques pratiqués sur des échantillons de tissus rénaux prélevés par biopsie. Les données cliniques recueillies au moment où les biopsies ont été pratiquées sont reprises au tableau I. Tous ces patients présentaient de la protéinurie et cinq d'entre eux étaient affligés d'une hématurie plus ou moins marquée. Aucun de ces malades ne présentait des signes cliniques évidents d'insuffisance rénale. Chez quatre malades atteints d'hématurie depuis une époque déjà éloignée, la présence de lésions glomérulaires a été constatée. Ces altérations sont considérées comme des séquelles d'un processus inflammatoire et les auteurs en discutent la classification. Chez deux malades, une seconde biopsie a été pratiquée après un intervalle de deux ans. Aucune aggravation des lésions histologiques n'a été constatée. Ces contrôles histologiques semblent devoir renforcer la thèse suivant laquelle le pronostic des troubles rénaux associés à un purpura anaphylactoïde n'est pas toujours défavorable, même dans les cas où l'on observe une hématurie persistante.

Nierenschädigung in Verbindung mit anaphylactoïder Purpura bei Kindern.

Sechs Kinder im Alter von 7 bis zu 15 Jahren mit anaphylaktoider Purpura und Mitbeteiligung der Nieren wurden untersucht. Die klinischen Befunde und Ergebnisse histologischer Studien an durch Nierenbiopsie gewonnenen Präparaten werden beschrieben. Sachdienliche klinische Daten aus der Zeit der Biopsie werden in Tabel I präsentiert. Alle Patienten hatten

Albuminurie und fünf unter ihnen hatten eine mehr oder weniger ausgesprochene Hämaturie. Keiner unter ihnen zeigte definitive klinische Anzeichen von Niereninsuffizienz. Bei vier Kranken mit langwährender Hämaturie wurden Schädigungen der Glomeruli gefunden. Diese Änderungen werden als Überreste eines entzündlichen Prozesses angesehen und ihre Klassifizierung wird erörtert. Bei zwei Kranken wurde eine weitere Biopsie nach einer Zwischenzeit von ungefähr zwei Jahren ausgeführt. Kein Fortschreiten der histologischen Läsionen wurde aufgezeigt. Die histologischen Studien scheinen die Auffassung zu unterstützen, dass die Prognose bei Nierenstörungen in Verbindung mit anaphylaktoider Purpura selbst bei Fällen mit anhaltender Hämaturie nicht ungünstig sei.

Lesiones renales asociadas con púrpura anafilatoide en los niños

Fueron examinados seis niños, de 7 a 15 años, con púrpura anafilatoide y signos de afectación renal. Se describen las observaciones clínicas y los resultados de los estudios histológicos de muestras obtenidas por biopsia renal. En la tabla I se presentan los datos más destacados de la clínica en el momento de la biopsia. Todos los pacientes aquejaban proteinuria y cinco presentaban hematuria más o menos acentuada. Ninguno evidenció signos clínicos definidos de insuficiencia renal. En cuatro de los pacientes con hematurias antiguas se hallaron lesiones glomerulares. Estas lesiones se consideran como restos de un proceso inflamatorio, discutiéndose su clasificación. En dos pacientes se efectuó una segunda biopsia al término de 2 años. No se demostró la progresión de las lesiones histológicas. Los estudios histológicos parecen apoyar la idea de que el pronóstico de las alteraciones renales asociadas con la púrpura anafilatoide puede no ser desfavorable aun en los casos con hematuria persistente.

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Serum Lipids in Infants with Progressive Cerebral Affection

by ERIK TERSLEV

Since Herman & Neumann (cit. Rafstedt) in 1912 had shown, that the content of cholesterol esters and that of neutral fat was lower in umbilical cord blood than in blood from adults, many investigations have been carried out concerning the different fractions of lipid in blood. In his thesis in 1955 Rafstedt went through the investigations published until then, and he concluded from his own work among others: In serum from umbilical cord blood the total lipids, total and free cholesterol and phospholipids are much lower than in sera from adults. During the first few days of life all the serum lipids increase steadily and on the fourth day they reach a level which is 80–90 per cent higher than at birth. During the rest of the first year the serum lipids fluctuate with a slight tendency to increase towards the end. During the age of 2–14 years the serum lipid values are higher than those of infants and fall within the ranges of the adult values.

Since then Adlersberg et al. in 1956 have reported an investigation from which it appears that cholesterol and phospholipids remain unchanged from 3 to 19 years of age in boys as well as in girls, only

hereafter rising and at that earlier in males, which is confirmed by an investigation carried out by Schaeffer et al. in 1958.

Table 1 gives a survey of the mean values of lipid analyses in infants and children from the most important investigations made since 1940, while Table 2 presents the adult values for comparison.

Material and Methods

The present investigation, the results of which hereby are introduced, was started with the purpose of finding out whether sera in children with progressive cerebral affection could demonstrate increased values of serum lipids, especially phospholipids, compared with sera of other children, analysed by identical methods and in the same laboratory. (The analyses were carried out by A/S Medicinsk Laboratorium, Copenhagen.) The determinations were made by the following methods: Total lipids by the method of Schoenheimer & Sperry (1934), phospholipids by G. Brun's method (1939) and cholesterol (total and free) by the method of G. C. Brun (1935). The analyses comprise sera from 50 children admitted to the Pediatric Department, University Clinic, Copenhagen, during the period March–December 1958. Fifteen of these 50 children suffered from progressive cerebral affection,

TABLE 1. *A survey of the mean values of lipid analyses in infants and children. From investigations made since 1940. Values in mg/100 ml.*

Authors	Year	Age	Total lipids	Phospho-lipids	Total chol.	Free chol.	Neutral fat
Rafstedt & Swahn	1954	1 month	591	130	138	50	
Radwin et al.	1940	2- 9 months	691	180	165		
Rafstedt	1955	1-12 months	606	188	130	40	
Radwin et al.	1940	1- 6 years	651	190	233		
Wamberg	1952	1- 6 years	804	196	182	55	
Thomas	1947	6-14 years	620	190	210	70	120
Radwin et al.	1940	6-16 years	600	170	186		
Kornerup	1948-50	1-16 years	820	195	209	57	
Rafstedt	1955	2-14 years	838	235	188	54	
Adlersberg et al.	1956	♂ 3- 7 years		227.1	179.8		
—	—	♀ 3- 7 years		261.9	209.0		
—	—	♂ 8-12 years		233.2	180.4		
—	—	♀ 8-12 years		241.7	196.4		

TABLE 2. *A survey of the mean values of the most important lipid analyses in adults. From investigations made since 1940. Values in mg/100 ml.*

Authors	Year	Age	Total lipids	Phospho-lipids	Total cholest-erol	Free cholest.	Total cholest./ phospho-lipids ratio	Neutral fat
Brun	1940		569	125	192	53.4		264
Peters & Man	1943	10-68		230	194			
Foldes et al.	1946	20-35		228	193			
Auken	1948	17-43	1038		200			
Ahrens	1950	21-38	475-725	219				
Kornerup	1950		836	180	218.8	57.5		
Russ et al.	1951			253			0.95	
Swahn	1952		740	33-805	184			
Petersen	1952			220				
Goldbloom	1952	♂ 20-55		208				
—	—	♀ 17-22		230				
—	—	22-72			197		1.10	
Swahn	1953	10-60	863	218				
Keys et al.	1954	20-55			221			
Gertler et al.	1954	♂ 18-35		193	197		0.98	
—	—	♀ 18-35		228	187		1.22	
Lindholm	1956	♂ 20-91	613-	245	175	66		
—	—	♀ 20-91	1488	252	182	68		
Adlersberg et al.	1956	♂ 18-22		217	185.2			
—	—	♀ 18-22		243.7	192.6			
Keating et al.	1957			224	214			
Schaefer et al.	1958	♂ 20-32		233.7-282.5				
—	—	♀ 20-32		243.1				

TABLE 3. *Serumlipids in the present material consisting of children from 3 months to 13 years of age.*

Age in years	Total lipids mg/100 ml	Phospho-lipids mg/100 ml	Phospho-lipids in % of total	Total cholest. mg/100 ml	Free cholest. mg/100 ml	Free cholest. in % of total	Neutral fat mg/100 ml	Cholest. phospholip. ratio
0-1	791 (668-1090)	180 (150-200)	23 (16-27)	194 (158-242)	44 (35-52)	23 (20-25)	414 (305-648)	1.07
1-2	759 (491-1100)	210 (85-380)	27 (17-35)	195 (117-290)	54 (32-118)	27 (23-42)	355 (265-446)	0.92
2-3	828 (631-1161)	208 (168-260)	26 (22-28)	213 (174-255)	55 (40-78)	25 (23-30)	407 (289-646)	1.02
3-4	1040 (712-1500)	217 (200-235)	23 (13-30)	196 (139-261)	49 (40-64)	25 (22-29)	627 (309-1161)	0.90
4-5	946 (840-1052)	255 (232-277)	27 (26-28)	261 (243-279)	62 (48-75)	24 (20-27)	431 (465-496)	1.02
5-6	717 (708-726)	179 (178-180)	25 (25-25)	203 (188-218)	45 (39-50)	22 (20-23)	335 (330-340)	1.16
6-7	759 (433-1021)	221 (105-308)	27 (24-30)	233 (89-331)	53 (26-73)	24 (21-29)	345 (239-411)	1.05
7-8	829 (698-959)	217 (195-238)	27 (25-28)	219 (196-241)	60 (43-76)	27 (22-32)	394 (307-480)	1.01
8-9	622 (578-666)	168 (143-192)	27 (25-29)	173 (161-185)	37 (32-41)	21 (20-22)	282 (274-289)	1.03
9-10	757 (717-826)	205 (185-240)	27 (25-29)	211 (192-221)	49 (44-55)	23 (22-25)	341 (312-379)	1.03
10-11	718 (635-850)	199 (163-243)	28 (26-30)	208 (171-249)	46 (38-55)	23 (22-24)	306 (265-358)	1.05
11-12 no cases								
12-13	757 (640-835)	193 (165-212)	26 (24-27)	224 (208-235)	52 (45-57)	23 (22-24)	340 (267-397)	1.16
13-14	680	175	26	134	37	28	371	0.86
Mean values	788 (433-1500)	202 (85-380)	26 (13-35)	205 (89-331)	49 (32-118)	24 (21-42)	373 (239-1161)	1.01
Neurot group I	856 (599-1161)	221 (193-277)	26 (22-29)	230 (171-279)	47 (38-78)	25 (22-30)	463 (265-646)	1.04
Neurot group II	820 (707-1044)	198 (150-308)	24 (16-29)	205 (158-290)	47 (35-69)	23 (20-25)	431 (318-570)	1.04
Other diseases	766 (433-1500)	195 (85-380)	26 (13-35)	196 (89-331)	47 (32-118)	24 (21-42)	371 (239-1161)	1.00

the remainders representing so various other diseases that they were considered quite adequate as "testmaterial". (By excluding 7 cases of fat dyspepsia and other types of dyspepsia from this "testmaterial" no deviation worth mentioning occurred as the values of these patients do not differ markedly from the values of the others.) The 35 children in the group with other diseases were selected through serial analyses in children on whom venous puncture for some other reason was done. In each analysis an amount of blood was used equal to 7-8 ml serum, all samples being collected in the morning before the first meal.

Results

Table 3 shows the mean values and distribution of serum lipids in the various agegroups in the present material. It is apparent that the values are in good agreement with previous determinations as well as with adult values and it is also evident

that all values remain constant with increasing age. A survey of the literature has not revealed any records of the mean values of neutral fat in children and adults apart from the two already mentioned (Table 1 and 2). The "neurological Group I" given in Table 3 comprises the severe cases in which it may be supposed, that a possible anomaly in the metabolism of the nervous system might appear: 5 severe cases of cerebral palsy, 2 of cerebral atrophy, 1 of cerebral tumor (brainstem-glioma) and 1 case of leucoencephalopathia progressiva, while "neurological Group II" includes 4 mild cases of cerebral palsy and 3 cases of Salaamcramp (Hypsarhythmia). The 3 cases of Salaamcramp have been placed in the "neurological Group II", because the signs of neurological disease were few and small, although the prognosis of their intelligence is bad.

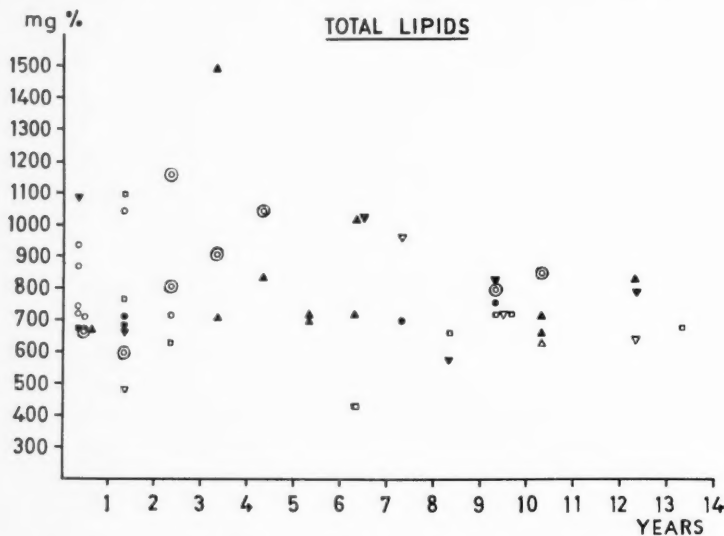


Fig. 1. Total lipid values in the present material comprising 50 children. ● Neurol. Group I. ▲ Infectious diseases. ○ Neurol. Group II. ▲ Endocrine diseases. ● Functional nervous disorders. ▼ Collagen diseases. ■ Herniae. ▼ Allergic diseases. □ Gastrointest. diseases.

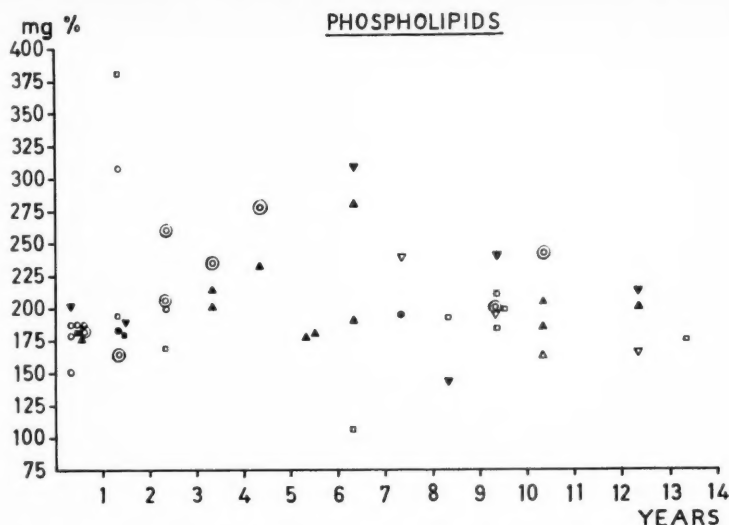


Fig. 2. Phospholipid values in the present material comprising 50 children. \bigcirc Neurol. Group I. Δ Infectious diseases. \bigcirc Neurol. Group II. \blacktriangle Endocrine diseases. \bullet Functional nervous disorders. ∇ Collagen diseases. \blacksquare Herniae. \square Allergic diseases. \square Gastrointest. diseases.

Values of the different lipid fractions are found to be a little higher in children with progressive cerebral affection than in children with other diseases, the increase being most pronounced in children with severe cerebral palsy, cerebral atrophy, cerebral tumor and leucoencephalopathia progressiva. However, this deviation—which does not concern any particular lipid fraction—is not significant, though at any rate it may strengthen the conviction that determinations of serum lipids is a possible factor in the efforts to obtain further elucidation of the chemical changes in progressive cerebral affections in children. No description with regard to the components of the different serum lipids in children with progressive cerebral affection has been found in the literature.

Figs. 1 and 2 show the distribution of the values of total lipids and phospholipids in

the present material with special regard to each group of disease—the spread of the other lipid fractions is smaller—and so it appears that only the group comprising severe cerebral palsy, cerebral atrophy, cerebral tumor and leucoencephalopathia progressiva shows a slight tendency to segregate. The values of the other disease groups show an even distribution, though a little more scattered during the first years of life than later on in childhood.

Conclusion and Summary

Sera from 50 children aged 3 months–13 years of which 15 suffered from progressive cerebral affection, the rest from other diseases, have been analysed with regard to the content of total lipids, phospholipids, total and free cholesterol and neutral fat. The values thus found are in good agreement with those found in normal

children and adults by other investigators. A slight increase of the lipid fraction values has been demonstrated in children with progressive cerebral affection com-

pared with children suffering from other diseases, but the difference is not significant and does not concern any particular lipid fraction.

Taux des lipides du sérum chez des bébés atteints d'affection cérébrale progressive.

Les sérums de 50 enfants âgés de 3 mois à 13 ans, dont 15 étaient atteints d'affection cérébrale progressive et le restant d'autres affections, ont été analysés au point de vue de leur teneur en lipides totaux, en phospholipides, en cholestérol total, en cholestérol libre et en graisses neutres. Les taux ainsi trouvés furent dans l'ensemble analogues à ceux relevés par d'autres auteurs chez des enfants et des adultes normaux. Une légère augmentation du taux des lipides a été observée chez les enfants atteints d'affection cérébrale progressive par rapport aux enfants atteints d'autres maladies, mais la différence n'a pas été significative et n'a intéressé aucune fraction particulière des lipides.

Serumlipoide bei Kindern mit fortschreitender Gehirnaffektion.

Seren von 50 Kindern im Alter von 3 Monaten bis zu 13 Jahren, unter denen 15 an einer fortschreitenden Gehirnaffektion und der Rest an anderen Erkrankungen litten, wurden mit Rücksicht auf ihren Gehalt an totalen Lipoiden, Phosphorlipoiden, totalem Cholesterol, freiem

Cholesterol und Neutralfett untersucht. Die so gefundenen Werte stimmen mit den bei normalen Kindern und Erwachsenen von anderen Untersuchern gefundenen überein. Eine geringfügige Steigerung in der Lipoidfraktion wurde bei Kindern mit fortschreitender Gehirnaffektion im Vergleich zu den an anderen Krankheiten leidenden beobachtet, aber der Unterschied ist nicht bedeutsam und betrifft keine besondere Lipoidfraktion.

Lípidos séricos en niños con trastornos cerebrales progresivos.

Se analizó el suero de 50 niños con edades comprendidas entre 3 meses y 13 años, de los cuales 15 presentaban trastornos cerebrales progresivos, el resto otras enfermedades, valorando el contenido total de lípidos, fosfolípidos, colesteroína total, colesteroína libre y grasa neutra. Los valores hallados concuerdan con los observados en niños normales y adultos por otros investigadores. Se demostró un ligero aumento de la fracción lipídica en los niños con trastornos cerebrales progresivos en comparación con los niños afectados de otras enfermedades, pero la diferencia no es significativa ni se refiere a ninguna fracción lipídica particular.

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The ABO Blood Groups and Disease in Infants and Children

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The possible relationship between the ABO blood group of the individual and his susceptibility to disease was first suggested by Alexander (1921).

Conducting his investigations on patients suffering from various forms of carcinoma, he came to the conclusion that those of Group B and AB were especially susceptible. Stimulated by these data Buchanan & Higley in the same year analysed the blood groups of 2446 patients of different nationalities suffering from a variety of diseases who attended the Mayo Clinic between the years 1917 and 1921. Their conclusions, however, were that there was no relationship between blood groups and malignancy as suggested by Alexander, that there was no relationship between blood groups and any disease, and that nationality should be taken into consideration in the presentation of statistical studies on blood grouping.

During subsequent years voluminous literature accumulated on the subject with rather unrevealing data, until Ugelli (1936) published his paper concluding that peptic ulceration predominated in individuals of Group O. In 1949 Lessa & Alarcao, analysing a large series of 500 patients with peptic ulcer confirmed Ugelli's results. In 1951 Struthers studied the blood groups of 400 infants who died at the Children's Hospital in Glasgow. Finding out that Group A was predominating and that a high percentage died of bronchopneumonia, he suggested that infants of Group A were more susceptible and those of Group O were more immune to

the disease. These conclusions, however, did not agree with those of Carter & Heslop who found out that the blood group distribution in bronchopneumonia did not differ significantly from that of the general population. In 1953 Aird, Bentall & Roberts made an extensive study of a large group of patients suffering from gastric carcinoma. Their results showed a highly significant association between the disease and Group A. Hollander obtained similar results. Encouraged by these positive findings, Aird, Bentall, Mehigan & Roberts extended their investigations on peptic ulcer and were once more able to confirm the relationship between the disease and Group O.

Since that date many articles on the subject have been published in various parts of the world. At present there is even more evidence that the association between Group O and duodenal ulcer is closer than that between Group O and gastric ulcer. It is also now agreed upon that pernicious anaemia is more prevalent in individuals of Group A. Similarly the association between Group A and diabetes mellitus was strongly suggested by Craig & Wang. In 1956 Mayr, Diamond, Levine & Mayr studied the blood group frequencies in patients suffering from brain tumours and pituitary adenomas. Though they obtained negative results in cases of brain tumours, a highly significant relationship between Group O and pituitary adenoma was noticed. In 1956 Billington investigated the records of 111 cases of portal cirrhosis with bleeding oesophageal varices. The results he obtained clearly

showed a marked increase in Group A. Plotkin was also able to demonstrate a significantly higher incidence of Group B in premature infants.

In addition to the previous data a large number of negative results appeared in the literature. Investigations were carried out on cancer of the colon, rectum, lung and breast with nonsignificant results. Toxaemia of pregnancy was similarly studied by Pike & Dickins and by Dickins, Richardson, Pike & Roberts and the combined data yielded a negative result. Maxwell & Maxwell found no association between blood groups and hypertension. Similarly Trobridge obtained negative results when he studied tuberculous patients. Investigations on rheumatic disease again revealed controversial data. Wilson and also Diamond found no association with a particular blood group. However, Buckwalter *et al.* claimed a predilection of Group 0 among rheumatic patients.

Attempts have furthermore been made to look for a relationship between the blood group and the severity of disease. Brown *et al.* found no appreciable difference between patients having bleeding or perforated ulcers and those with uncomplicated ones. Buckwalter and associates similarly found no difference between peptic ulcer patients having high free hydrochloric acid and those having low one. However, Brown *et al.* noticed a particularly higher excess of Group 0 in patients suffering from anastomotic or stomal ulcers.

Method

Four disorders of infancy and childhood were selected for the present investigation. These were rheumatic disease, bronchial asthma, mental retardation and infantile wasting. It was intended to find out if a predilection occurred with a particular blood group.

Rheumatic Disease: Blood groups were determined in 70 children with rheumatic disease. These included active and inactive

cases of cardiac and arthritic rheumatism. **Bronchial Asthma:** 51 infants and children presenting with the condition were studied. **Mental Retardation:** A group of 73 children was investigated. It included four mongols and 69 cases of primary amentia with an I.Q. ranging from 47 to 77. **Infantile Wasting:** Though different from the first three disorders in lacking a previously suggested constitution, infantile wasting was included in the present work. It was thought possible that some other factor in addition to diarrheal disorders and undernutrition could be predisposing for the rapid development of the condition in some infants. A group of 143 cases was studied and in all of them wasting developed after one or more attacks of gastroenteritis.

Blood grouping tests were performed on a porcelain spot plate. A drop of Anti A serum was added to one drop of blood and a drop of Anti B serum to another. After mixing, the suspensions were allowed to stand at room temperature for five minutes and then examined for macroscopic clumping. Only about 1% of the samples were found to require microscopic confirmation.

Results

The distribution of blood groups among Egyptians was determined by a number of workers (Abdoush & Dewi, Matta and others). The results obtained in the present investigation were statistically compared with those of Abdoush & Dewi. They studied a large group of 10,045 individuals and their figures were accordingly used as our controls. Table 1 presents the ABO grouping data they obtained, Table 2 shows the results of the present study and Table 3 demonstrates a statistical comparison between the two.

Rheumatic disease: It can be seen from Table 2 and Table 3 that Group 0 forms 22.8% of the series. The difference between this percentage and that of the

TABLE 1. *The percentage distribution of blood groups in Egyptians (Abdoush & Dewi).*

Percentage of Group A	Percentage of Group B	Percentage of Group AB	Percentage of Group 0	Total
35.54 ±.04 %	24.37 ±.08 %	7.45 ±.16 %	32.64 ±.1 %	10,045

TABLE 2. *The distribution of blood groups in rheumatic disease, bronchial asthma, mental retardation and infantile wasting.*

Disease	Group A		Group B		Group AB		Group 0		Total
	N°.	%	N°.	%	N°.	%	N°.	%	
Rheumatic disease	24	34.3	24	34.3	6	6.8	16	22.8	70
Bronchial asthma	12	23.5	20	39.2	7	13.7	12	23.5	51
Mental retardation	29	39.7	17	23.2	4	5.5	23	31.6	73
Infantile wasting	50	34.9	38	26.8	25	17.4	30	20.9	143

TABLE 3. *Statistical comparison between the blood group distribution in controls and that in rheumatic disease, bronchial asthma, mental retardation and infantile wasting.*

Groups compared	Test for difference			
	Group A	Group B	Group AB	Group 0
Controls and Rheumatic disease	P > .05	P > .05	P > .05	P < .05
Controls and Bronchial asthma	P > .05	P < .05	P > .05	P > .05
Controls and Mental retardation	P > .05	P > .05	P > .05	P > .05
Controls and Infantile wasting	P > .05	P > .05	P < .05	P < .05

controls is shown to be significant. Comparison between the other blood group percentages, however, shows a nonsignificant result.

Bronchial asthma: Table 2 and 3 show that 39.2 % of the infants and children

under investigation belonged to Group B. Comparison between this percentage and that of the controls revealed a significant difference.

Mental retardation: The percentage frequencies obtained in this group are respec-

tively 39.7 % Group A, 23.2 % Group B, 5.5 % Group AB and 31.6 % Group O. The difference between these figures and those of the controls is shown to be statistically nonsignificant.

Infantile wasting: Table 3 shows that the percentage distribution of Group O is significantly lower than it is in the controls. The difference between the percentages of Group AB was also found of statistical significance.

Discussion

The positive association between the ABO blood groups and disease may suggest a number of possibilities. It may be simply an observation secondary to stratifications within the population. It may also be due to a pleiotropic effect of the blood group gene different from that of its role in determining the presence of the antigen (Roberts). Thirdly, it may truly depend upon the physical presence of the blood group substance.

The results of the present study seem to suggest that: 1) Children of Group O are possibly more immune to rheumatic disease. 2) There is a possible association between Group B and bronchial asthma. 3) There is no relationship between blood groups and mental retardation. 4) Infants of Group O are possibly more resistant to develop wasting and those of Group AB are more susceptible.

It seems unlikely that these variations are due to stratifications. All the groups investigated were apparently homogeneous. This is in addition to the fact that more evidence is now pointing towards homogeneity of populations as regards their blood grouping. The explanation of

such apparent susceptibility or immunity of infants and children belonging to certain blood groups to diseases is by no means clear. It can be only suggested that they may be inherited characteristics. It was found in the present investigation that individuals of Group O are more resistant to develop rheumatic disease and infantile wasting. Struthers similarly found that bronchopneumonia is less prevalent in infants of Group O. As wasting usually develops after a diarrhial disorder following an attack of gastroenteritis, it may be cautiously postulated that individuals of Group O are possibly more immune to certain infections. It is obvious, however, that large groups and high significancies are necessary before more certainty can be attached to blood group relationships. It is sometimes unlikely that at one centre such large groups are available. Accordingly, it is advisable to publish the results of all investigations which though possibly not individually adequate for analysis could be added to others and thus serve to make more definite conclusions.

Summary

1) A short review of the relationship between the ABO blood groups and disease is given.

2) The ABO blood group frequencies were determined in infants and children suffering from rheumatic disease, bronchial asthma, mental retardation and infantile wasting.

3) It is suggested that: a. Children of Group O are possibly more immune to rheumatic disease. b. There is a possible relationship between bronchial asthma and Group B. c. Infants of Group O are pos-

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such apparent susceptibility or immunity of infants and children belonging to certain blood groups to diseases is by no means clear. It can be only suggested that they may be inherited characteristics. It was found in the present investigation that individuals of Group O are more resistant to develop rheumatic disease and infantile wasting. Struthers similarly found that bronchopneumonia is less prevalent in infants of Group O. As wasting usually develops after a diarrhial disorder following an attack of gastroenteritis, it may be cautiously postulated that individuals of Group O are possibly more immune to certain infections. It is obvious, however, that large groups and high significancies are necessary before more certainty can be attached to blood group relationships. It is sometimes unlikely that at one centre such large groups are available. Accordingly, it is advisable to publish the results of all investigations which though possibly not individually adequate for analysis could be added to others and thus serve to make more definite conclusions.

Summary

1) A short review of the relationship between the AB0 blood groups and disease is given.

2) The AB0 blood group frequencies were determined in infants and children suffering from rheumatic disease, bronchial asthma, mental retardation and infantile wasting.

3) It is suggested that: a. Children of Group O are possibly more immune to rheumatic disease. b. There is a possible relationship between bronchial asthma and Group B. c. Infants of Group O are pos-

sibly more resistant to develop wasting and those of Group AB are possibly more susceptible. d. There is no relationship between mental retardation and blood groups.

Groupes sanguins ABO et maladie chez le nourrisson et l'enfant

Un bref examen des rapports entre les groupes sanguins ABO et quelques maladies est fait ici. La fréquence du groupe sanguin fut déterminée chez des nourrissons et des enfants souffrants de maladie rhumatismale, d'asthme bronchique, de retardement mental et de dépérissement infantile. On peut suggérer que a) les enfants du groupe O sont probablement moins sensibles aux maladies rhumatismales, b) qu'il y a une relation probable entre l'asthme bronchique et le groupe B, c) que les nourrissons du groupe O sont probablement plus résistants au dépérissement infantile et que ceux du groupe AB y sont probablement plus susceptibles, d) qu'il n'y a pas de relation entre le retardement mental et les groupes sanguins.

ABO-Blutgruppen und Krankheiten bei Kleinkindern und Kindern

Es wird ein kurzer Überblick über die Beziehungen zwischen den Blutgruppen des ABO-Systems und gewissen Krankheiten gegeben. Dabei wurde die ABO-Blutgruppenhäufigkeit bei Kleinkindern und Kindern, die an rheumatischen Krankheiten, Bronchialasthma, geistiger Unterentwicklung und infantiler Atrophie litten,

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bestimmt. Es wird angenommen: a) daß Kinder der Gruppe O möglicherweise immuner gegen rheumatische Krankheiten sind; b) daß eine mögliche Beziehung zwischen Bronchialasthma und Gruppe B besteht; c) daß die Kinder der Gruppe O wahrscheinlich widerstandsfähiger gegen infantile Atrophie sind und die der Gruppe AB möglicherweise anfälliger; d) daß keine Beziehung zwischen geistiger Unterentwicklung und den Blutgruppen besteht.

Los grupos sanguíneos ABO y las enfermedades de infantes y niños

Se presenta un corto resumen de las relaciones existentes entre los grupos sanguíneos del sistema ABO y las enfermedades, determinándose la frecuencia de los grupos sanguíneos A, B, AB y O en los infantes y niños que padecían enfermedades reumáticas, asma bronquial, retraso mental y atrofía infantil. Se sugiere: a) que los niños del grupo O son posiblemente más inmunes a las enfermedades reumáticas; b) que existe una relación posible entre el asma bronquial y el grupo B; c) que los infantes del grupo O son posiblemente más resistentes al desarrollo de la atrofía y los del grupo AB probablemente más propensos a este mal; d) que no existe ninguna relación entre el retraso mental y los grupos sanguíneos.

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CASE REPORT

A Case of Idiopathic Hypoproteinaemia

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Idiopathic hypoproteinaemia is a rare condition. Since only a few cases have been published and since the disease presents a number of obscure problems regarding aetiology and pathogenesis, the following case will be reported.

A boy, aged 9 months, was admitted to the Paediatric Department of the Odense County and City Hospital on March 21, 1958. He was an only child. His parents were in good health, he had been born at term and normally delivered, cried immediately, and did not show any abnormalities during the neonatal period. The baby was exclusively breast fed for 5 months, had a mixed diet during the next three months, and on admission he was receiving an adequate diet consisting of milk, meat, fish, and vegetables plus a supplement of vitamins A, D and C since the age of 5 months. During the past two months an extra supplement of A and D had been given (1600 I.U. daily).

Ever since birth, the patient had been apt to show periocular swelling when crying. His mother had not noted any tendency to oedema in other sites. The weight gain each month had always been at the upper limit of normal, during the first 4 months 1000-1200 g, and during the months prior to admission about 500 g. Otherwise, his development had been normal. He could sit at 5 months and stand when supported 2½ months later.

Six weeks prior to admission the patient suddenly developed loose, aqueous, foul-

smelling, and mucous stools, about 10 movements daily. During this attack he had a seizure of tonic convulsions of the limbs, head bent backward and a tendency to cyanosis around the mouth. On the next day he had a similar episode. Each lasted for 2 or 3 minutes.

Since the onset of diarrhoea, the periocular swelling had increased, but his mother had not yet noticed any tendency to swelling elsewhere.

On admission, the baby was feeble, pale, with fairly severe periorbital oedema as well as lumbar oedema. His longitudinal growth was normal—70 cm—and nutritional state good, rather ample on the lower part of the body, but the trunk was rather lean and the lower legs slightly oedematous. There was a slight hepatomegaly, the margin of the liver being palpable 2-3 cm below the costal border, but no other abnormalities.

Immediately after admission, the patient had a short seizure of convulsions with upward rotation of the eyeballs, jerky contractions in all limbs, and a tendency to cyanosis of the lips. The seizure subsided spontaneously, and there were no further episodes of this nature. The oedema present on admission subsided within the first week, and has not returned.

A tetanic position of the hands and feet was observed after April 18, being at first intermittent but later persistent for several days.

Throughout the stay in Hospital the boy had frequent, loose, bulky, watery, foul-

smelling stools, but not with a visible fat content. The number of daily movements fluctuated from 2 to 11, as a rule 5-7. The amount excreted by the rectum was fairly constant, about 400-500 g. On standing, the stools separated into two layers, the lower sediment consisting apparently of loose, but otherwise normal-looking faeces, and above a looser, somewhat glistening layer with a trace of foam, and in between the two layers there was a clear yellowish fluid.

Laboratory findings: Weight 10,050 g. Tuberculin test (Moro) negative.

Urine: During the entire stay in Hospital, apart from a few days, the daily output of urine was between 100 and 250 ml, specific gravity max. 1030. Neither proteinuria nor glycosuria occurred at any time. Micr. exam. of urine: No abnormality. Sulkowitch test negative.

Determination of the amino acids in the urine showed moderate quantities of cystine in addition to glycine, serine, glutamic acid, glutamine, alanine, threonine, valine, leucine, phenylalanine, tyrosine, histidine, lysine, taurine, and traces of a few other amino acids. The amino acid content was estimated to be considerably in excess of normal.

Blood:	Minimum value	Maximum value
E. S. R. mm/hr	1	12
Haemoglobin	100	136
Leucocytes	13,640	22,100
Lymphocytes (% of leucocytes)	6	12
Blood urea	29 mg %	41 mg %
Serum creatinine	0.44 mg %	
Serum bicarbonate	10 mEq.	27 mEq.
Serum calcium	3.5 mg %	5.5 mg %
Serum phosphorus	2.2 mg %	2.8 mg %
Serum phosphatase	4.3	10.6
	(Buch U.)	

Serum proteins:

	Total protein	$\beta + \alpha_1$	α_2	β	γ
26.3	3.3 %	46 %	22.1 %	16.8 %	15 %
1.5	2.9 %	41 %	22.3 %	23.2 %	13.5 %

Other blood studies: Serum chloride 107-108 mEq., serum potassium 3.2 mEq., serum cholesterol 127 mg/100 ml. Bone marrow aspiration (twice): A count of 2000 mononuclear elements did not reveal any plasma cells. Other findings normal.

Stools: The faecal excretion of fat ranged from 2.3-4.5 g in 24 hours. During the days prior to collecting the faeces the patient had received a diet consisting of equal parts of gruel and milk. The quantity of fat ingested with this diet was estimated to range from 9 to 15 g, so about 33 % of the fat intake was excreted with the stools. Ninety-four per cent of the excreted quantity was fatty acid.

Culture from the faeces showed growth of coli 26 during the first few days, but later no pathogenic intestinal bacteria. On repeated occasions the stools contained trypsin.

Spinal fluid: Total protein 50 mg/100 ml. Calcium concentration in spinal fluid 3.9 mg/100 ml.

The 17-ketosteroid excretion in the urine was normal (1.9 mg/24 hours).

Electrocardiography showed no definite abnormality apart from fairly tall T waves in Leads I and II.

Chest radiography showed on admission an ill-defined infiltration posteriorly in the cardio-diaphragmatic angle. Follow-up radiogram 6 weeks later showed no abnormality.

Radiographic examination of the wrists and ankles as well as long bones showed no abnormality apart from pronounced halisteresis and marked narrowing of the corticalis.

Treatment: A low-salt diet, protein milk with rice flour, altered later because of the stools to protein milk with arabin. Because of the stools the diet was also altered, for a short period, to exclusively gruel, later with a supplement of milk. Due to the low serum calcium values, the boy was given calcium lactate by the oral and calcium gluconate by the intramuscular route from April 8 to May 1. The low serum albumin values were treated with intraosseous injections of concentrated human serum albumin. After the first episode of cyanotic marbling, steroid therapy was given from April 11 to April 27,



Fig. 1.

owing to the alarming condition; at first with hydrocortisone and corticotrophin, continued later with prednisone 5 mg \times 3.

During this period he was also given blood transfusions. From Apr. 22, calciferol was started, 300,000 Units daily for three days, then 100,000 Units daily. On this medication the tendency to tetany grew less marked, and the serum calcium increased (3.5–4.5 mg/100 ml). During this period the urine was submitted daily to the Sulkowitch test which was constantly negative.

During some periods achromycin and penicillin were given.

The condition gradually deteriorated. The patient had—especially during the terminal phase—many episodes of generalized cyanotic marbling, cool limbs, and a frequent pulse. During these episodes he would be irritable and whimpering. On May 3rd–4th an abscess developed on the left buttock at the site of the repeated injections of calcium gluconate. It was incised on May 5, and about 50 ml thick, yellowish pus was evacuated. During the following days the temperature rose to a maximum of 39.6°C, the patient became even more debilitated and died on May 10.

Except during short periods, the body weight had been constantly falling, being on 5th May 7900 g.

Post-mortem findings: Liver of normal size. Surface smooth and glistening, cut surface pale grey with mottled pattern on some sections. The consistency was a little firmer than normal. Microscopic examination of the liver showed no abnormalities. The kidneys were grossly as well as microscopically normal. The lungs were normal apart from the right upper lobe which was atelectatic, mottled on section, and where microscopic study revealed widespread pneumonic changes. The lesion was of a hyperacute nature and probably an agonal phenomenon. The thyroid, parathyroid, and adrenal glands were normal. So were the heart, stomach, and intestines. The spleen was grossly normal, but on microscopic examination the lymphatic tissue was found to be under-developed, appearing everywhere atrophic and rudimentary. Nowhere a trace of any reaction centre. Plasma cells were not demonstrable despite special staining and study for demonstrating such cells. Only a few lymph nodes showed slight enlargement. The gland-

ular structure was preserved, and as in the spleen there were no reaction centres. Plasma cells were also not demonstrable in the lymph nodes.

Discussion

The persistent abnormal findings in the present case were marked (1) hypoproteinaemia, (2) hypokalaemia, (3) relative lymphopenia and absence of plasma cells in the bone marrow, in addition to (4) frequent watery, loose and foul-smelling, slightly fatty stools as well as (5) weight loss. On the other hand, no signs of renal or hepatic damage could be found despite repeated investigations. Autopsy failed to show any pathological changes in these organs, but there was atrophy of the lymphatic system and absence of plasma cells.

The possibility of primary disturbance of the calcium metabolism suggests hypoparathyroidism, but the low serum phosphorus militates against it. On the contrary, the decreasing phosphorus values might indicate something like increasing secondary hyperparathyroidism. There is no reason to assume that the patient's diet at home had been low in calcium, and in Hospital he had an ample supplement of calcium by mouth as well as by the parenteral route, but without avail.

Rickets is ruled out by the normal phosphatase values and the X-ray findings.

A primary gastrointestinal disorder does not appear likely. Microscopic investigation of the faeces at a time when the diet comprised only gruel showed that it contained moderate quantities of fat. Steatorrhoea, hypocalcaemia, as well as hypoproteinaemia may be observed in coeliac disease, but we feel that this possibility

may be excluded, as the patient did not present the clinical characteristics of this disease; nor were the stools at any time suggestive of coeliac disease, not even on a more fatty diet. On repeated occasions, the stools proved to contain trypsin. The history also indicates that the disease has been present from birth, whereas the diarrhoeas did not appear until 6 weeks before admission. The fact that the seizures started at the same time as the diarrhoea also indicates that the hypocalcaemia has pre-existed. Summing up, it may be stated that the symptoms and signs cannot be assigned to any known nosological entity in the group of gastrointestinal disorders.

This leaves only the syndrome designated as idiopathic hypoproteinaemia. This condition has been described in great detail in connection with case reports by Jonsson & Lagercrantz, Ehrengut, Debré, and others.

Hypoproteinaemia being the sole constant sign raises the question whether all the symptoms and signs are explicable on the basis of the low serum protein level. Most authors have found agreement between the serum protein values and the oedema, increasing serum protein values tending to be accompanied by a subsidence of the oedema and vice versa. It is more difficult to explain the other changes (especially the intestinal symptoms and the hypocalcaemia) as results of the hypoproteinaemia alone. According to Debré, however, long-standing hypoproteinaemia may entail changes of the liver, pancreas, and intestine with secondary reduction of enzymic activity and reduced intestinal motility which might explain the diarrhoea. Certainly, the pronounced hypocalcaemia is the sign which is most difficult

to explain on the basis of hypoproteinaemia alone. Although hypoproteinaemia always tends to decrease the protein-bound part of the serum calcium and this may explain the moderate fall in serum calcium in most cases, our patient and Debré's had calcium values too low to be explicable exclusively by the low serum protein. As also pointed out by Debré, it cannot be ruled out that the hypocalcaemia may be in a way secondary to the gastrointestinal disturbances, due to the formation of insoluble limesoaps. When considering our case, it seems difficult to conclude that the hypoproteinaemia alone could have been responsible for all the symptoms and signs. In the first place, the oedema subsided during the first week in hospital without demonstrable increase in serum proteins. Later, there was a slight increase, but in the terminal stage again a drop without attendant oedema or weight gain. In the second place, we repeatedly demonstrated pronounced enzymic activity (trypsin) in the stools. Finally, lymphopenia is a fairly constant phenomenon in idiopathic hypoproteinaemia, while it is not encountered in other types of hypoproteinaemia.

The cause of the idiopathic hypoproteinaemia remains obscure. Among the possibilities which have been discussed there is (1) reduced intestinal absorption, (2) hepatic disease, (3) reduced protein synthesis, and (4) increased destruction of protein. The first explanation is unacceptable, since growth and thriving—apart from the terminal stage—and Hb level are normal and the patients do not bear the marks of any deficiency condition. Moreover, some authors have found a positive nitrogen balance. Some workers as-

sume the presence of sub-clinical hepatic damage, supporting their assumption on the post-mortem findings, but as already stressed by Debré the liver changes are not pronounced enough to be responsible for hypoproteinaemia. They should rather be considered secondary, since similar hepatic changes may be encountered in hypoproteinaemia of other, known causes.

Comparing nephrosis and idiopathic hypoproteinaemia, Ehrengut believes that in both instances there is dysproteinaemia due to the synthesis of abnormal serum protein. He thinks that albuminuria in nephrosis is due to this factor, not to a primary renal disease.

To illustrate yet another pathogenetic explanation, it may be mentioned that Bille & Vahlquist have published two cases showing—in addition to hypoproteinaemia and oedema—signs of reduced activity in the external function of the pancreas. Their cases exhibited no trypsin activity, considerably reduced lipase activity, and little increase in blood amino acid nitrogen following tolerance test with gelatin. Their patients were treated with pancreatic enzymes with favourable effect, the oedema subsiding and the plasma protein values returning to normal. By comparison with similar cases of idiopathic hypoproteinaemia these authors substantiated that not infrequently the cause is a disturbance of the external pancreatic function. They emphasize, therefore, that this possibility has to be considered, even in the absence of definite clinical evidence of cystic pancreatic fibrosis. In our case repeated investigations revealed pronounced trypsin activity in the stools, and 94% of the excreted fat was split.

Schwartz & Thomsen have reported J¹³¹

studies in a case of idiopathic hypoproteinaemia, and their results indicate, in a convincing manner, that in their case there was an increased destruction of the albumin fraction. This assumption is supported by Cattell who set up the concept "metabolic rate", i.e. the proportion of plasma albumin broken down per day. Cattell found this rate to be increased in patients with idiopathic hypoproteinaemia, reflecting increased destruction of protein. Since the serum protein showed normal values in the cases of Schwartz & Thomsen as well as Cattell, it had to be assumed that the albumin synthesis too was considerably increased.

Gitlin's studies on the serum protein metabolism showed, however, that some cases of idiopathic hypoproteinaemia are conditioned by reduced synthesis. Whether the primary feature is increased destruction or reduced synthesis can only be decided by determining, in each individual case, the breakdown curve of labelled albumin.

From a pathogenetic point of view, the most interesting findings in the present case were the pronounced absence of plasma cells in the bone marrow as well as in the spleen and lymph nodes and the marked hypoplasia of the lymphatic system. Since plasma cells are presumably factors in the synthesis of protein fractions other than gamma globulins, and since marked lymphopenia is a sign described fairly often in idiopathic hypoproteinaemia, these two factors must be assumed to be of essential significance in the patho-

genesis of this peculiar syndrome which still presents so many unelucidated problems.

Summary

A fatal case of idiopathic hypoproteinaemia in a boy, aged 9 months, is reported. Ever since he was born, the boy was said to have shown swelling around the eyes after crying. Six weeks before admission, he suddenly began to have loose, watery, foul-smelling, and mucous stools. In the course of this attack, he had a seizure of tonic convulsions lasting for 2 or 3 minutes. During the stay in hospital, his condition was marked by frequent, often prolonged episodes of tetany, a persistent weight loss, and by gradual deterioration of general health. Furthermore, he had serum protein values about 3-4%, albumin constituting about 45%, hypocalcaemia, relative lymphopenia, frequent loose and watery stools, and no plasma cells in the bone marrow aspirate. On the other hand, the urine did not contain albumin, and hepatic function tests were normal.

Autopsy revealed pronounced hypoplasia of the lymphatic apparatus. Just as in the bone marrow aspirate, plasma cells were not demonstrable either in the lymph nodes and spleen, even despite a special staining technique.

It is emphasized that pronounced hypoplasia of the lymphatic system and the absence of plasma cells in bone marrow, lymph nodes, and spleen must be considered of significance to the development of idiopathic hypoproteinaemia.

Un cas d'hypoprotéinémie idiopathique

Rapport sur un cas mortel d'hypoprotéinémie idiopathique chez un garçon de neuf mois. Depuis sa naissance, l'enfant présentait une enflure autour des yeux après avoir pleuré. Six semaines avant son admission à l'hôpital il commença à avoir des selles molles, liquides, d'odeur nauséabonde et muqueuses. Pendant cette crise il eut une attaque de convulsions toniques d'une durée de deux à trois minutes. Son séjour à l'hôpital, fut marqué par des attaques fréquentes et assez prolongées de tétanie, par une perte persistente de poids, et par une détérioration graduelle de son état général. En outre il avait un taux de protéines du sérum d'environ 3-4 %, 45 % d'albumine, une hypocalcémie, une lymphopénie relative, des selles fréquentes et liquides et pas de plasmocyte dans la moelle osseuse. D'autre part l'urine ne contenait pas d'albumine et les tests de fonction hépatique étaient normaux. L'autopsie a montré une hypoplasie prononcée de l'appareil lymphatique. Comme dans la moelle osseuse, on n'a pu détecter de plasmocyte ni dans les ganglions lymphatiques, ni dans la rate, bien qu'une technique spéciale de colorants ait été appliquée. On attire l'attention sur le fait qu'une hypoplasie prononcée du système lymphatique et l'absence de plasmocyte dans la moelle osseuse, les ganglions lymphatiques et la rate doivent être considérés comme des facteurs importants dans le développement de l'hypoprotéinémie idiopathique.

Ein Fall von idiopathischer Hypoproteinämie

Es wird über einen letalen Fall von idiopathischer Hypoproteinämie bei einem Jungen von 9 Monaten berichtet. Seit seiner Geburt soll er Schwellungen um die Augen gezeigt haben, wenn er geweint hatte. Sechs Monate vor seiner Einlieferung hatte er plötzlich losen, wäßrigen, faulriechenden und schleimigen Stuhl. Im Verlauf dieser Unregelmäßigkeit hatte er einen Anfall von tonischen Konvulsionen, die 2 oder 3 Minuten andauerten. Während seines Krankenhausaufenthaltes war sein Zustand durch häufige, oft längere Tetanieepisodes, einen andauernden Gewichtsverlust und eine allmähliche Verschlechterung des allgemeinen Gesundheitszustandes gekennzeichnet. Außerdem hatte er

Serumproteinwerte von 3-4 %, Albuminbesandteile von ungefähr 45 %, eine Hypokalzämie, eine relative Lymphämie, häufig losen und wäßrigen Stuhl und keine Plasmatozyten im Markaspirat. Andererseits enthielt aber der Urin kein Albumin; die Leberfunktionsprüfungen waren normal. Die Autopsie ergab eine starke Hypoplasie des Lymphsystems. Genau wie im Markaspirat konnten weder in den Lymphknoten noch in der Milz Plasmazellen nachgewiesen werden, auch trotz Anwendung einer besonderen Färbetechnik. Es wird betont, daß die starke Hypoplasie des Lymphsystems und die Abwesenheit von Plasmatozyten im Knochenmark, in den Lymphknoten und in der Milz als für die Entwicklung der idiopathischen Hypoproteinämie wichtig angesehen werden müssen.

Un caso de hipoproteinemia idiopática

Se informa sobre un caso fatal de hipoproteinemia idiopática en un niño varón de 9 meses. Siempre desde que nació, se dijo que mostraba hinchazón alrededor de los ojos después de llorar. Seis meses antes de ingresar, empezó a tener de repente deposiciones blandas, acuosas, de olor putrefacto y de consistencia mucosa. En el transcurso de este ataque, tuvo un acceso de convulsiones tónicas de aproximadamente 2 a 3 minutos de duración. Durante su estancia en el hospital, su estado se caracterizó por frecuentes y a menudo prolongados períodos de tetania, una pérdida persistente de peso y por el empeoramiento gradual de la salud general. Además, presentaba valores de seroproteína alrededor del 3 al 4 %, albúmina alrededor del 45 %, hipocalcemia, linfemia relativa, frecuentes deposiciones blandas y acuosas, así como una falta absoluta de plasmotocitos en el aspirado medular. Por otra parte, la orina no contenía albúmina y las pruebas de la función hepática dieron resultados normales. La autopsia reveló una hipoplasia pronunciada del sistema linfático. Igual que en el aspirado medular, no pudieron hallarse plasmotocitos ni en los ganglios linfáticos ni en el bazo, incluso a pesar de aplicarse una técnica especial de coloración. Se subraya que la pronunciada hipoplasia del sistema linfático y la ausencia de plasmotocitos en la médula ósea, en los ganglios linfáticos y en el bazo han de considerarse de importancia para el desarrollo de la hipoproteinemia idiopática.

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CASE REPORT

Wissler's Syndrome

Report of a Case

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Wissler (21) in 1944 described a morbid state under the name of subsepsis hyperergica, characterized by intermittent fever, varying exanthema, neutrophilic leucocytosis with a shift to the left, and transitory joint phenomena in children. Owing to the intermittent fever, which did not respond to salicylate treatment, Wissler supposed the picture to be that of a special syndrome related to, but not identical with rheumatic fever. Fanconi (4) reported a similar complex of symptoms, which he called subsepsis allergica Wissler, since described under this name or as Wissler-Fanconi's syndrome (2, 3, 5, 6, 7, 9, 10, 12, 13, 14, 15, 16, 17).

Present case

An eleven-year-old boy, born 14/8/1947. No familial predisposition to rheumatism or allergic diseases. Birth and development normal. Admitted in 1949 to the Epidemic Unit for infectious mononucleosis.

From 1951 to 1958 he had ten admissions to hospitals with a total stay in hospital of 1072 days on account of his present disease. During most of these stays there was found redness of the fauces, intermittent fever, uncharacteristic punctate non-hemorrhagic exanthema ranging in duration from some hours to some days, and transitory pain or swelling of the wrists, knee-joints, or ankles.

During the intervals at home between the admissions the patient occasionally had attacks of fever and pain in the joints of short duration.

During the stays in hospital he was treated with ACTH; in 1951 and 1953 with good effect; in 1956 with some effect. In 1952 he was given acetylsalicylic acid with good effect, and again in 1954 with some effect. In 1954 and in 1956-7 the patient was treated with cortisone, which, however, in 1956-7 had to be supplemented by acetylsalicylic acid to obtain freedom from symptoms.

During most of the stays in hospital he received antibiotics, with no effect whatever. Prior to his latest admission in 1958 he was given 300,000 i.u. of penicillin V daily prophylactically for about 12 months. Fig. 1 illustrates the course and treatment in 1958.

Sternal punctures in 1952 and 1953 revealed a shift to the left of the granulocytic elements. Biopsy specimens taken from skin and muscle in 1953 showed no changes. Histologic examination of a lymph gland showed subacute-subchronic lymphadenitis. The results of laboratory tests are recorded in Table 1.

Discussion

The triad of fever, pain in the joints, and exanthema is encountered both in infectious diseases and in collagen diseases.

TABLE 1. *Laboratory findings.*

Year of admission	1951	1952	1953	1953	1954	1954	1955	1956	1956/57	1958
Number of days	139	83	47	114	86	75	74	111	202	141
Hemoglobin g/100 ml	9.6	9.3	11	9.5	9.6	11.8	11.5	12.7	11.7	11.7
Sedimentation rate mm/hour (minimum)	110	123	84	112	98	36	65	96	97	101
White blood count (max.)	40,400	21,100	18,700	17,900	22,300	12,400	12,300	24,300	27,800	17,400
neutrophils (max.) %	83	86	79	64	78	56	72	88	88	85
eosinophils (max.) %	5	1	1	1	0	3	1	5	3	1
Antistreptolysin units/ml (max.)	220	4000	450	125	180	360	450	70	65	110
Antistreptococcaluronidase test, units/ml (max.)		9000	<2000	4000	<2000	<2000	4000	3000	<2000	<2000
alpha-Staphylococcal toxin test, units/ml (max.)				0		4		<2		8
Antistaphylococcaluronidase test, units/ml (max.)										<2
Agglutination with hemolytic streptococci	0		0		0			pos.	0	0
Weil-Vidal seroreaction			0					0	0	
Wassermann test			0							
Gonocoe complement fixation test								0	0	
Blood culture	0	0	0	0	0					
Total protein in serum g/100 ml (max.)		7.8						6.4		6.8
albumin + alpha ₁ g/100 ml		3.12						3.68	3.57 + 0.51	
alpha ₂		1.25						1.07		0.90
beta		0.89						0.72		0.76
gamma		2.55						0.93	normal	1.07
Roentgenogram of heart	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal
" " ankles					normal	normal		normal		
" " wrists					normal					
" " teeth										
Electrocardiogram	normal	normal	normal	normal	normal	normal	normal	normal	normal	normal
L.E. cells in blood		0								0

The former group can rather easily be distinguished clinically and serologically, but the previously used diagnosis: febris maculosa intermittens probably included infectious and collagen diseases (19). Among the collagen diseases lupus erythematosus disseminatus, Schönlein's pupura, rheumatic fever, and rheumatoid arthritis may cause difficulties in the differential diagnosis, but skin biopsy, the appearance of the exanthema, and the course exclude the two first-mentioned diseases.

In rheumatic fever and rheumatoid arthritis it may happen that only the progressive course of the disease reveals the diagnosis (18). It may therefore, in cases of a short duration of illness be extremely difficult to differentiate with certainty Wissler's syndrome from these two diseases. This was true of Bernheim *et al.*'s (2) three cases, Garby's (7) third case, Keyzer's (13) two cases, and four of Wissler's (20, 21) cases. Of the other cases reported, Wissler's (20) third case and Monnet *et al.*'s (15) second case must be regarded as rheumatoid arthritis.

However, a number of cases remain in which, despite a protracted course, no permanent changes have been demonstrated in the heart or the joints. The syndrome is accordingly not identifiable as rheumatic fever or rheumatoid arthritis.

In addition to the stated triad, there has in all cases been found a raised E.S.R. (maximally 130 mm/hour), and a neutrophilic leucocytosis (maximally 52,000 white blood cells and 96% neutrophils). Eosinophilia (17) has only been reported in one case. Nowak (16) also observed leucopenia and considerable lymphocytosis. In our case we found: E.S.R. maximally 123 mm/hour, white blood cells maximally 40,400, neutrophils maximally 88%, and eosinophils maximally 5%.

In some instances there have, in addition, been reports of a moderately enlarged spleen (15), glandular swelling (14, 15, 17), nephropathy (3, 9, 12, 15), hepatitis (3, 12, 14), pleuritis (3), pericarditis (9, 19). None of these phenomena were present in our patient.

Blood cultures were negative in all the cases examined. A streptococcal antibody test was performed in six cases (3, 7, 15), but a rise was observed in only three (3, 7). Our patient presented a raised antistreptolysin titre during the first 5 years, but it was normal in the last 3 years.

Of the patients described so far, the youngest was 18 months old (14), and the oldest 12 years (12) at the time of onset of the disease. Duration of the disease: from 4 months (12) to 5 years (3, 7). Our patient was 3½ years old at the onset of his symptoms, and the disease has been of nearly 8 years' standing thus far. Boys and girls seem to be affected with the same frequency.

Treatment: one patient improved on cortisone (3), one on pyramidon (14), two on tryptaflavin (12, 19), one on salicylates (15), and two (4, 17) following vaccine treatment (streptococcus vaccine). Our patient responded favourably to ACTH, while cortisone had some effect, and acetylsalicylic acid a varying effect. Antibiotics have never been found effective.

The *etiology* is unknown, but most writers regard the complex of symptoms as an allergic reaction. Nowak (16) claimed to have demonstrated food allergy in two cases. Grislain *et al.*'s (9) case developed 3 days after a fifth diphtheria-tetanus vaccination. In Fanconi's (4) case there was a history of bronchitis and tonsillitis, and streptococcal strains were cultured from an extracted tooth. In Denys' (3) case there was likewise a history of angina, and our patient was on nearly all admissions, found to have red and swollen fauces. Furthermore, there was demonstrated in our case a raised antistreptolysin titre, and later a raised alpha-phyllococcus-antitoxin titre.

As stated previously, blood culture has never shown any bacteria, and the disease

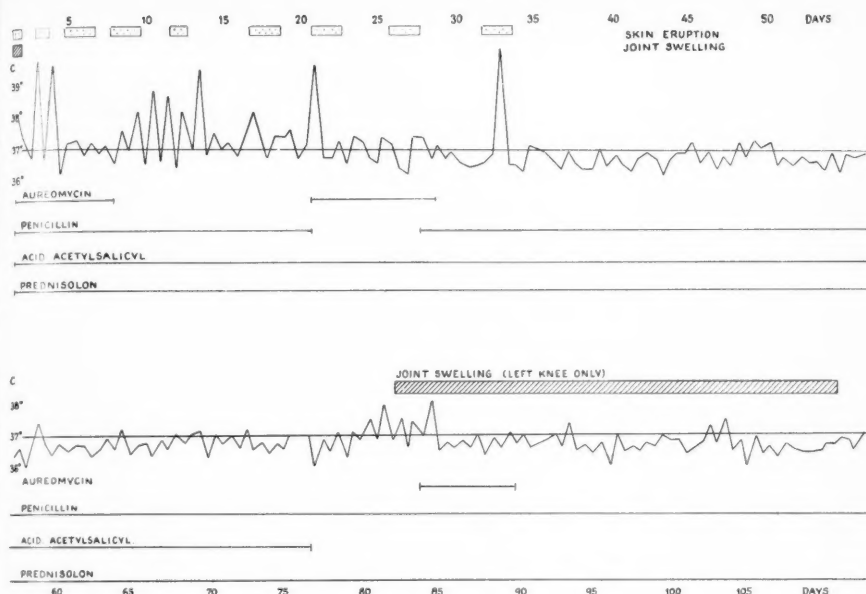


FIGURE 1 FROM ADMISSION IN 1955

Fig. 1.

is not likely infectious (though, perhaps, bacterio-allergic). The name of subsepsis, applied by Wissler (21) and later by Fanconi (4) is therefore inappropriate. Denys (3) proposes instead pseudosepsis allergica, while Nowak (16) prefers the term allergosis sepsiformis.

Opinion is divided as to whether Wissler's syndrome is to be regarded as a separate entity (9), or as an atypical course of rheumatic fever (8), or of rheumatoid arthritis (5), or as a pre-arthritis precursor of rheumatoid arthritis (3). Denys' (3), Garby's (7) and Keyzer's (13) cases are remarkable in that typical rheumatoid arthritis developed after a fairly long period of freedom from symptoms. Sury (18) in his thesis, reported five cases of rheumatoid arthritis, which definitely support the last-mentioned theory.

Fanconi (4) places the syndrome between rheumatic fever and rheumatoid arthritis, with transitional forms to both diseases.

Janbon *et al.* (10), on the other hand, regard rheumatic fever, Still's disease, and Wissler's syndrome as the same disease, only with different locations: heart, joints, and skin respectively.

Forte (6) calls attention to the resemblance of the syndrome to Schönlein's purpura. This disease occasionally occurs without purpura developing (1), as the fragility of the capillary wall depends on the degree of reaction to the toxic agent (11). Since, however, neither purpura nor hematuria have been described in association with Wissler's syndrome, despite a prolonged course of illness, these diseases must be supposed to differ qualitatively.

Our case does not contribute towards a solution of the problem, but is remarkable in having begun as typical rheumatic fever associated with a raised concentration of

streptococcal antibodies in the blood over a period of several years. On recurrence a few years ago the disease manifested itself with the same symptoms as previously, but now without a raised blood level of streptococcal antibodies. The fairly protracted involvement of the left knee in 1958 (*vide* Fig. 1) seems, however, to suggest rheumatoid arthritis.

The prolonged hormone treatment may possibly have modified the picture of the disease.

Syndrome de Wissler-Fanconi.

Depuis l'âge de 3½ ans, un garçonnet de 11 ans a été hospitalisé à de nombreuses reprises à la suite de fièvres intermittentes, d'exanthèmes aspécifiques et d'arthralgies qui ne s'accompagnaient ni de troubles cardiaques ni d'altérations articulaires chroniques. Le diagnostic présumé est celui d'un syndrome de Wissler-Fanconi. Revue et discussion de la littérature.

Wissler-Fanconi'sches Syndrom.

Ein 11-jähriger Junge war, seit er 3½ Jahre alt war, mehrere Male wegen intermittierenden Fiebers, uncharakteristischen Exantheams und

Summary

An 11-year-old boy has since the age of 3½ years been admitted to hospital several times (total stay 1072 days) on account of intermittent fever, uncharacteristic exanthema, and pain in the joints, with no associated heart involvement or chronic joint changes. The diagnosis is presumably one of Wissler's syndrome. The literature is reviewed and discussed.

Gelenkschmerzen ohne Herzerkrankung oder chronische Gelenkveränderungen ins Krankenhaus aufgenommen worden. Diagnostisch handelt es sich vermutlich um das Wissler-Fanconi'sche Syndrom. Das Schrifttum wird erörtert.

Síndrome de Wissler-Fanconi

Un niño de once años había sido ingresado repetidas veces en el hospital desde la edad de 3 años y medio por fiebre intermitente, exantema atípico y dolor articular, sin que se asociaran trastornos cardíacos ni alteraciones articulares crónicas. El diagnóstico es probablemente el de síndrome de Wissler-Fanconi. Se revisa y se discute la bibliografía.

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CASE REPORT

Primary Carcinoma of the Liver and Giant-Cell Hepatitis in Infancy

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Malignant epithelial tumors of the liver are—although rare (33)—the most common carcinomas of infancy and childhood (14, 37). This relatively frequent occurrence has been ascribed by Roth & Duncan (44) to a supposed etiological relationship between primary liver carcinoma in infancy and giant-cell (neonatal) hepatitis, probably of viral origin. Roth & Duncan (44) reported a case of a girl with jaundice since 5 weeks of age who at 7 months was found by liver biopsy to have giant cell hepatitis. She died at 2 years and 9 months of age with primary carcinoma of the liver. Viral hepatitis has also been suggested as a carcinogenic stimulus in primary liver carcinoma in adults (4, 24, 40, 41).

This is the second case report in the literature of primary carcinoma of the liver following neonatal giant-cell hepatitis. There are some noteworthy features in addition to those of the case of Roth & Duncan (44). A brother had previously died with intrahepatic bile duct atresia (congenital or post-inflammatory) when 7 months old after a history of jaundice since the age of 3 weeks. A third sibling was stillborn.

A preliminary report of the patient and her brother (16, 17) was prompted by the remarkable occurrence of almost identical clinical histories of the two siblings resulting from two apparently different, pathologic processes in the liver, neonatal giant-cell hepatitis, and partial atresia of the intrahepatic bile ducts (congenital or post-inflammatory). The underlying cause in both cases was tentatively supposed to be a transplacental infection with serum hepatitis virus (SH virus); the mother was assumed to be a healthy carrier of the virus (21, 48). In this more detailed report the etiology and pathogenesis of the hepatic lesions in the two cases are scrutinized in light of some new aspects on giant-cell hepatitis (6, 15, 25, 35, 39, 48, 56), and primary liver carcinoma in connection with giant-cell hepatitis of infancy is discussed.

Case report

Case 1. (E.Å.)

The patient was a girl, born in December, 1954. The mother was 23 years old. Pregnancy and delivery at term were normal, birth weight 2820 g. She was breast-fed and thrived well until 3 weeks of age when she

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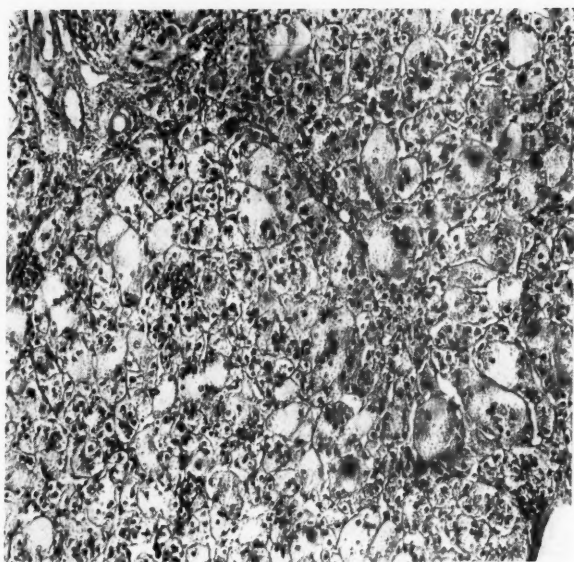


FIG. 1. Case 1. Photomicrograph of the liver at 11 weeks of age, showing the characteristic picture of a giant-cell hepatitis. The alterations engage all parts of the lobule uniformly (central vein in the lower right corner; portal space in the upper left). van Gieson $\times 110$.

became pale, tired, and developed vomiting and bleeding tendency (melena and purpura). She was brought to the Pediatric Clinic in Umeå and was found to have a severe hypoprothrombinemia. During the first day in the hospital her condition deteriorated. She had convulsions and the fontanel was tense, and blood-stained fluid was obtained at lumbar puncture. The lower edge of the liver was palpated 1–2 cm below the costal margin. There was a moderate bilirubinemia, about 3 mg/100 ml serum, the direct van den Bergh test was reported as ++, and the serum alkaline phosphatases were elevated. WBC was 16,500 and ESR (Westergren method) 19 mm. After treatment with vitamin K, penicillin, sedatives, and blood transfusions, the patient's condition improved. A few days later, at 4 weeks of age, a progressive jaundice appeared.

At 7 weeks of age she was admitted to the Pediatric Clinic in Upsala, mainly for surgical exploration of the bile ducts. Her serum

bilirubin value was then 13.4 mg/100 ml; negative reactions were obtained with the cephalin-cholesterol flocculation test and the thymol turbidity test. The value for serum alkaline phosphatases was elevated (40 Buch-Buch units). Prothrombin and total serum proteins were within normal limits. The serum lipid content was slightly above normal. The urine contained bilirubin but no urobilinogen. There was no bile pigment in the stools. The Wasserman reaction, the tests for toxoplasmosis, and the direct Coombs' tests were negative. There was no spherocytosis, and the osmotic fragility of the erythrocytes was normal.

When the patient was 11 weeks old, an exploratory laparotomy was performed. The liver was found to be slightly enlarged and dark greenish. The extrahepatic bile ducts were normal on cholangiography. The gall bladder contained bile. A wedge-shaped surgical excision was made from the lower edge of the liver.

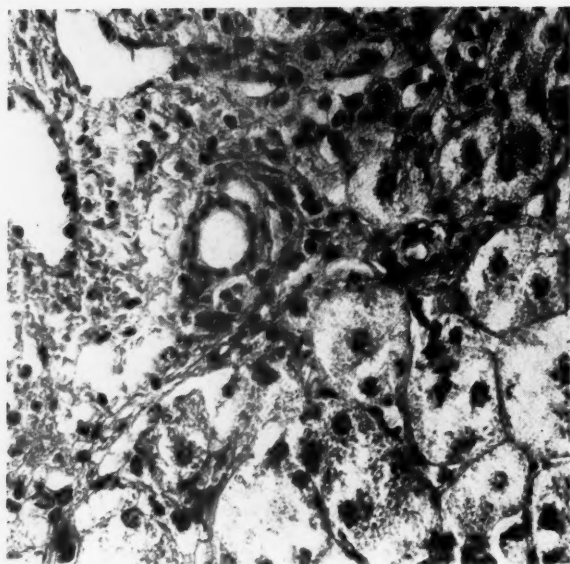


Fig. 2. Case 1. Higher magnification of the periportal area in Fig. 1, showing a normal interlobular bile duct (center). van Gieson $\times 440$.

Microscopic examination of the biopsy specimen showed the typical picture of giant-cell hepatitis (Figs. 1 and 2). The lobular pattern was preserved and there was no fibrosis. Almost all parenchymal cells were severely altered, and many multinucleated giant cells were visible. They contained much bile pigment and some glycogen. There was no iron-positive pigment in the liver parenchymal cells, but some in the Kupffer cells. The bile ducts in the portal spaces were normal (Fig. 2).

The laparotomy was uneventful and the girl was discharged from the Clinic after 1½ month. Her condition was rather stationary for a few months, but gradually the jaundice decreased, and the girl slowly gained weight again. When she was 5 months old, her general condition was fairly good and only a yellow tinge of the sclerae remained of the jaundice. The serum bilirubin value was about 2 mg/100 ml at that time.

The girl developed normally, but jaundice never disappeared completely. She had some

pruritus and periods with dark urine and clay-colored stools. The jaundice was often aggravated in connection with intercurrent infections. At the age of 2½ years she had one of the most severe of these bouts of jaundice. Her serum bilirubin value was then 18 mg/100 ml but soon returned to the usual values between 1 and 2 mg/100 ml.

At the age of 2 years and 9 months, the girl was admitted to the Pediatric Clinic in Upsala for a follow up. Her condition was fairly good, but the sclerae were yellow and the serum bilirubin value ranged between 3.6 and 5.6 mg/100 ml. The liver showed greater enlargement than previously. The serum alkaline phosphatases were elevated (73 Buch-Buch units, later 40 units) but the flocculation tests were normal. A splenoportography showed normal conditions. Two percutaneous needle biopsy specimens, one in each lobe of the liver were taken.

Microscopic examination (second biopsy): The same kind and extent of changes were

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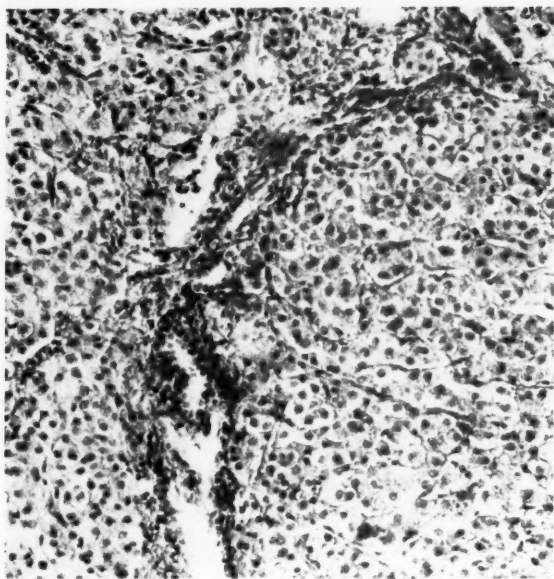


Fig. 3. Case 1. Photomicrograph of the liver at 2 years and 9 months of age showing almost complete restitution of the parenchyma. The selected area is from a periportal space without any pathologic changes. (In other parts there were portal fibrosis and some bile casts in the bile capillaries in the central parts of the lobules.) van Gieson $\times 200$.

found in the two biopsy specimens. The material was scanty and showed only slight changes in the liver parenchyma (Fig. 3). The lobular pattern was intact. Most of the liver cells were normal and only a few giant cells were found. There were, however, signs of cholestasis with a moderate number of bile casts in the canaliculi in the central parts of the lobules. Some of the portal spaces were enlarged, with some connective tissue infiltration in the periportal parts of the lobules. There was only sparse occurrence of bile pigment in the liver parenchymal cells. The bile ducts in the portal spaces were normal and only a slight round cell infiltration occurred. The anatomic diagnosis was "portal fibrosis" (3).

The girl's condition remained on the whole stationary until she was 3 years and 5 months old. Then she began to lose weight, jaundice increased and was progressive. Ultimately

she got dyspnea and died at the age of 3 years and 7 months, apparently from suffocation.

Gross findings at autopsy: The body was that of a 3½-year-old emaciated girl, weighing 13,000 g. There was a distinct icteric tint in the skin and the sclerae. No xanthomatosis was observed. There was no increased amount of fluid in the abdominal cavity.

The liver weighed 1750 g (normal, 418–516 (9)). Most of the right lobe was occupied by confluent grey-whitish tumor nodules, measuring up to 2 cm in diameter (Fig. 4). They were of a rather soft consistency and were not umbilicated. The uninvolved parts of the liver were dark green, tough and somewhat gritty at cutting. There were no coarse cirrhotic nodules. Some tumor invasion of branches of the portal vein was noted. The extrahepatic biliary tract was normal. The gall bladder contained bile.

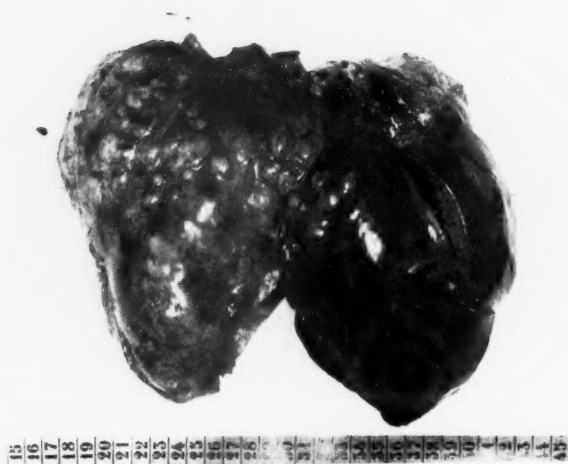


Fig. 4. Case 1. Ventral-cranial aspect of the liver at autopsy. The right lobe is studded with tumor nodules bulging out on the serosal surface. Note absence of umbilication. The left lobe is fairly intact, smooth, without any large cirrhotic nodules.

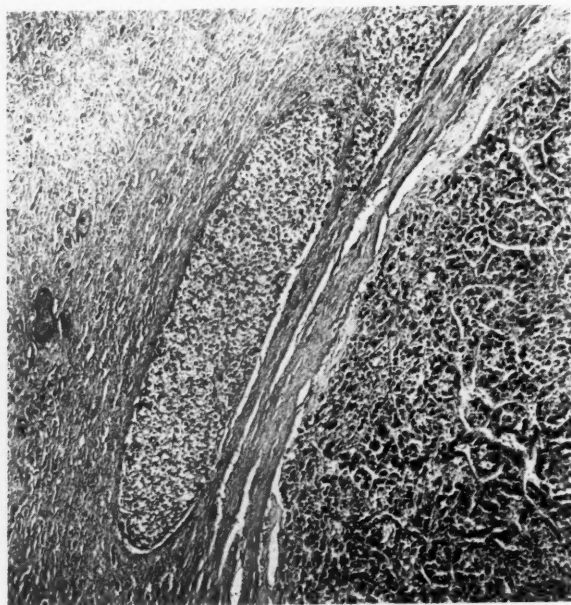


Fig. 5. Case 1. Low-power photomicrograph of two tumor nodules in the liver, one showing the trabecular pattern of a primary liver carcinoma with scanty, capillary stroma (lower right), and the other a more solid growth pattern (center). The surrounding liver parenchyma is densely fibrotic, van Gieson $\times 44$.

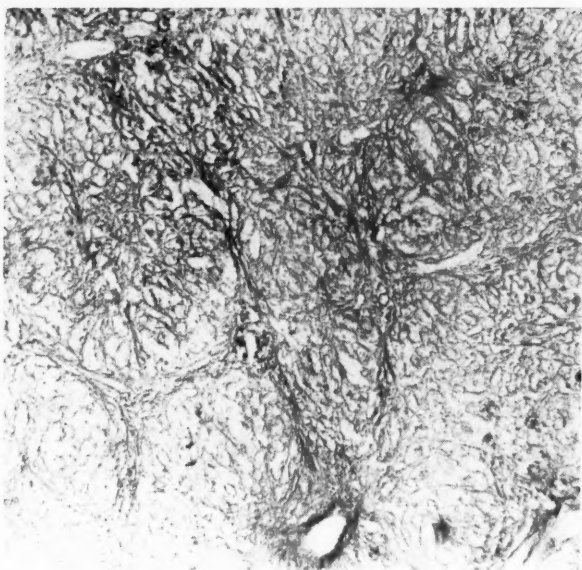


Fig. 6. Case 1. Reticulin pattern of a region of the liver uninvolved by tumor, showing a monolobular portal cirrhosis. Laidlaw $\times 48$.

The lungs were studded with metastatic tumor nodules, measuring up to 1 cm in diameter. The bronchi were compressed and there was very little air-containing parenchyma.

The spleen weighed 400 g (normal, 37-38 (9)). It was dark red and firm, showing chronic venous congestion. There were varices in the lower third of the esophagus, and markedly widened veins in the thoracic cavity, around the liver, stomach, and spleen.

The remaining autopsy findings were irrelevant.

Microscopic findings (autopsy material):

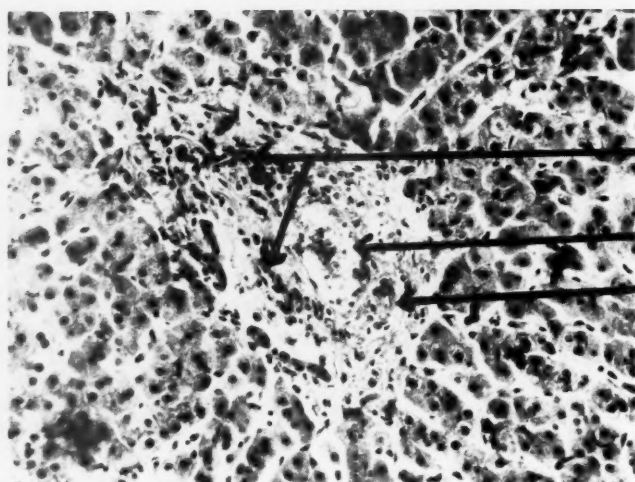
The tumor nodules of the liver and the lungs showed the characteristic features of a trabecular liver cell carcinoma, Grade II-III (14) with a scanty, capillary stroma (Fig. 5). The cancer cells were moderately large. The cytoplasm was slightly acidophilic and the nuclei were rather hyperchromatic and occupied a fairly large part of the cell. The

cancer cells contained a moderate amount of bile pigment and showed some fatty change. Intravascular growth occurred frequently. There was no calcification and no teratoid structures.

The uninvolved regions of the liver showed advanced collagenous monolobular portal cirrhosis (13) (Fig. 6). There was plenty of bile casts, extensive bile duct proliferation, and many multinucleated cells containing bile pigment. No intranuclear inclusion bodies were found.

Case 2. (B.A.)

A brother of Case 1 was born at term in September, 1953. The birth weight was 3180 g. Prenatal, obstetrical and postnatal history was essentially normal. The boy was breast-fed. He had a slight jaundice during the first week after birth. Two weeks later he got an upper respiratory infection and began to lose weight and vomit. At the age



Lymph vessels (L)

Branch of portal vein

Branch of hepatic artery

Fig. 7. Case 2. Medium power view of a representative portal space in the liver. The branches of portal vein and hepatic artery are clearly seen (arrows) but a typical interlobular bile duct is not found (cf. Fig. 2). van Gieson $\times 220$.

of 5 weeks he got worse with hematemesis, melena and purpura, and was admitted to the Pediatric Clinic in Umeå.

On admission he had a slight jaundice. The lower edge of the liver was palpated 2–3 cm below the costal margin. He had a severe hypoprote thrombinemia. During the first day in hospital his condition grew worse, he got convulsions and a tense fontanel was palpated. At lumbar puncture the cerebrospinal fluid was hemorrhagic. WBC was 21,300 and ESR (Westergren method) 25 mm. The serum bilirubin value ranged between 3 and 8 mg/100 ml the next few days. The direct van den Bergh reaction was reported as $++$. The flocculation tests were normal but the serum alkaline phosphatases were elevated (27 Buch-Buch units). The Wasserman reaction was negative, and there were no signs of hemolytic disease. The serum lipids were not investigated. The urine contained bilirubin but no urobilinogen or urobilin. There was bilirubin in the stools.

After a few blood transfusions his condition improved, although the values for WBC

ranged between 9700 and 23,400 and for ESR between 20 and 50 mm. There was a progressive lymphocytosis (81% at discharge). Jaundice had almost completely disappeared when he left hospital at the age of 2½ months. The serum bilirubin value was then about 1 mg/100 ml. The clinical diagnosis was acute hepatitis.

At 4 months the jaundice had disappeared completely. There was, however, still some leukocytosis (WBC 18,000) with lymphocytosis (70%). ESR was 14 mm/hour.

When the boy was 6½ months old, he again became jaundiced with pruritus, dark urine, and clay-colored stools. He was not hospitalized until a month later, when he got fever and diarrhea. WBC ranged between 14,200 and 29,400 and the ESR between 15 and 20 mm/hour. On admission he was in a bad condition and died within a few days at the age of 7 months and 3 weeks with the clinical picture of hepatic insufficiency.

Gross findings at autopsy: The body weighed 4860 g. The skin and sclerae were



Fig. 8. Case 2. High power view of the liver showing numerous bile casts (arrows) and intracellular bile pigment. van Gieson $\times 800$.

moderately icteric. There were no bruises or skin xanthomas.

The abdominal cavity did not contain any excess fluid. The liver was slightly enlarged, smooth, brownish green, and of a rather soft consistency. There were no signs of fatty change, cirrhosis, or tumor on the cut surface. The gall bladder contained bile and the extrahepatic bile ducts were normal.

Apart from moderate pulmonary edema, the remaining gross findings were non-significant.

Microscopic findings (autopsy material):

There were surprisingly slight pathologic alterations in the liver. The lobular pattern was preserved and the parenchymal cells were normal apart from some accumulation of bile pigment intracellularly. No giant cells were observed. There was only a slight to moderate round cell infiltration in the portal spaces, which were not conspicuously widened. The large bile ducts were normal without bile accumulation. The small bile ducts, however, did not appear normal. In the pertaining portal areas, only branches of the portal vein and the hepatic artery were

found together with slitlike spaces lined by flattened endotheliumlike cells (Fig. 7). It could not be established whether the slitlike spaces were lymph vessels or altered bile ducts. In the lobules there were signs of bile stasis which was definitely more intracanalicular than intracellular, showing plenty of bile casts (Fig. 8). This type of cholestasis indicates that bile could not pass through the portal spaces showing no normal bile ducts. We think that these changes indicate partial atresia of intrahepatic bile ducts.

Two fairly small pieces were available from the liver of Case 2. Quantitative data of the supposed intrahepatic bile duct atresia are given in Table 1.

When the control liver sections were assessed for "atretic" bile ducts the same criteria were not used as when the slides from our Case 2 were investigated. "Atretic" bile ducts were assessed in the control sections as soon as any doubt existed on the presence of a normal interlobular bile duct, e.g. when the lumen of the bile duct could not be discerned or was distorted by technical artefacts, tangential sectioning and the like. In the liver sections from Case 2 "atre-

TABLE 1. *Percentage of portal spaces with "atretic" bile ducts.*

Liver specimen	Per cent portal spaces with "atretic" bile ducts	Mean (per cent)
Case 2 piece a)	59 (52/88)	67
Case 2 piece b)	76 (50/66)	
Control 1*	22 (25/113)	25
Control 2**	27 (29/108)	

* 8-month-old boy dead from pneumonia.

** 6½-month-old boy dead from pancreatic fibrosis.

tic" bile ducts were recorded only when no traces of epithelium-lined lumina were found in the portal spaces. This mode of approach was chosen in order to minimize the possibility that the supposed intrahepatic bile duct atresia of Case 2 would be a mere delusion, originating from agonal, post-mortem, technical, or other changes. Consequently the figures from the controls are "maximum values" and give no information of "normal" occurrence of atretic bile ducts in this age period.

It is obvious from Table 1 that there is a significantly higher incidence of bile duct atresia in the two specimens from the boy's liver than in the controls. There was no fatty change and no iron-positive pigment in the parenchymal cells of the boy's liver.

The anatomic diagnosis was partial intrahepatic bile duct atresia, postinflammatory or congenital.

Stillborn child

A third sibling, a girl, was born at term in April, 1956. She was apparently dead already a few days before delivery. The umbilical cord was wrung tightly in four loops around the neck and in one loop around a leg. The cause of the death was supposed to be intrauterine strangulation.

Gross findings at autopsy: Weight 2800 g, no jaundice, no signs of maceration. The

liver was of ordinary appearance and dark red-brown. No signs of fatty change, cirrhosis or liver disease. The gall bladder and the extrahepatic bile ducts were normal. Apart from subpleural petechiae and dark, homogenous, non-aerated lungs the remaining gross findings were negative.

Microscopic findings on autopsy material: The liver was autolyzed to such a degree that no histologic diagnosis was possible.

The Parents

Both parents were in good health and had not had any serious diseases. The mother had never had jaundice and "liver function tests" were normal. She had never been a blood donor, nor received transfusions. The serologic tests for syphilis were negative for both parents. There was no evidence of hemolytic anemia.

The blood groups were reported as follows:

Father: A₁ Rh(-)

Mother: O Rh(-), type Rh₁ Rh₁

Boy: A Rh(+)

Girl: A₁ Rh(+)

Third sibling: not determined.

In March, 1955, the mother's blood was tested serologically for blood group incompatibility. There was no Rh incompatibility but immune anti-A antibodies (56) were found. These antibodies could not be detected in a new investigation in the beginning of June, 1955.

In each delivery the placenta seemed normal and without defects at inspection made by the midwife.

Discussion

Present views on the etiology of giant-cell hepatitis

Giant-cell (neonatal, fetal, infantile) hepatitis is said to show rising frequency (4, 19, 36). The same is also true for infantile (genuine, congenital, familial, juvenile) cirrhosis (18) which may be the final stage of giant cell hepatitis (25). Most authors

seem to agree that the lesion is a true viral hepatitis, acquired *in utero* by transplacental passage of one of the two known types of hepatitis virus (5, 11, 13, 20, 22, 47, 48). Epidemic hepatitis (endemic, infectious, viral A, IH hepatitis) stimulates the production of antibodies and its virus is not known to be able to pass the placental barrier (2, 42, 46, 48). Serum hepatitis (viral B, SH hepatitis) does not stimulate the production of antibodies, its virus can pass the placental barrier, and the disease is known to occur in the neonatal period (8, 21, 48).

Others tend to refute the theory of viral etiology (6) and suggest incompatibility of some rare or unknown blood groups (15, 31). The attribution of giant cell hepatitis to iso-immunization disease (15, 31) has, however, been criticized (39). "Toxic" damage *in utero* by some undefined agent has also been proposed (32). Still others consider giant-cell hepatitis to be a congenital malformation (49). This view has also been criticized (12, 39). The comparatively frequent familial occurrence has suggested a genetic etiology (25, 50). Degenerative changes of the placenta have been proposed as being of causal importance (35).

Etiology of Case 1

In the present Case 1, the direct Coombs' test was negative, but immune anti-A antibodies were present for some months after delivery. Consequently the possibility of a blood group incompatibility must be considered (56). The girl and the boy showed no obvious clinical signs of disease due to blood group incompatibility (21, 56) during the first week after birth.

There was no iron-positive pigment in the liver cells (15). The temporary occurrence of immune anti-A antibodies in the mother's serum is not necessarily a sign of ABO immunization but may be explained by a placentitis (7). Pregnancy was normal. We could find no malformation of the bile capillaries in the two biopsy specimens from the girl's liver. No changes of the placenta were visible.

Thus, viral etiology seems plausible in our Case 1. The incubation period of serum hepatitis is 1½–6 months. The girl showed the first clinical signs of liver disease about 3 weeks after birth. It thus seems justified to consider the giant-cell hepatitis in our Case 1 as being acquired *in utero*. It is true, however, that we have no positive evidence that the mother was a carrier of SH virus.

Morphology of different stages of giant-cell hepatitis

Rather scanty information is available about the sequence of morphologic changes of giant-cell hepatitis when the time of survival after the acute disease extends over years (4, 10, 45). It is known that 60–70 per cent of the patients recover without clinical sequelae and the rest develop cirrhosis or die in the acute stage (20, 25). To our knowledge there are no reports on repeated liver biopsies after the height of the disease. In our Case 1, one liver biopsy was obtained in the acute phase of the disease and another 2½ years later when the patient was in a fairly good condition. The latter biopsy indicated almost complete restoration of a previously severely altered liver parenchyma (Figs. 1–3), although some portal fibrosis and

cholestasis occurred in our case. Ten months later, however, there was advanced cirrhosis (Fig. 6).

Relation between primary liver carcinoma, cirrhosis, and giant-cell hepatitis

In adults, the common precursor of liver cell carcinoma is cirrhosis of the liver (14, 24, 27, 30, 33, 41, 54). In infancy and childhood, on the other hand, liver cell carcinoma is infrequently associated with cirrhosis (4, 14, 33). In their recent review, McDougal & Gatzimos (33) stated that among the more than 100 cases of hepatocellular carcinoma reported in infants and children, cirrhosis was noted in only 7. (No preceding giant-cell hepatitis was established.) They considered it probable, however, that when cirrhosis is present, the relationship between cirrhosis and hepatocellular carcinoma in infants and children is similar to that in adults. The same opinion has also been advanced by others (4, 27). The monolobular portal cirrhosis found at autopsy in our case was regularly distributed throughout the liver parenchyma (Fig. 6). The needle biopsy specimens taken 2½ years after the acute phase of the giant-cell hepatitis may therefore be considered representative for the organ as a whole. Consequently, both the cirrhosis and the carcinoma probably developed during the last 10 months of the girl's life. The clinical course of liver cell carcinoma, when associated with cirrhosis, is notoriously short. The average duration of life is 3-4 months from the onset of symptoms (14). Thus the carcinoma in the girl's liver most likely developed during the last few months when her condition grew worse.

The case reported by Roth & Duncan

(44) showed great similarity with our own. However, they stated that it was improbable that the hepatic tumor had developed secondarily to the cirrhosis present at autopsy. The time interval (2 years) was believed to be too short. They assumed a direct etiological relationship between the viral giant-cell hepatitis and the primary liver cell carcinoma. This opinion is difficult to understand. It is known that a post-hepatic cirrhosis can develop within a few months (3, 10). Moreover, the second liver biopsy in our case showed that the giant liver cells had disappeared and, consequently, no direct transformation from altered liver cells to real tumor cells was seen. The giant liver cells present in the cirrhotic liver at autopsy are believed to be part of the usual regenerative changes found in advanced liver cirrhosis.

Etiology of Case 2

No definite etiological or pathogenetic diagnosis of the liver disease was arrived at Case 2. The boy was hospitalized for too short a time to make possible a thorough laboratory examination and the post-mortem material available was insufficient for a satisfactory analysis of the case. The following features, however, indicate a post-inflammatory atresia (34, 55) of some of the intrahepatic bile ducts rather than a congenital malformation (agenesis) (1, 23, 38).

It is known from histologic descriptions of the cholangiolitic type of viral hepatitis seen in adults and children (39, 43, 55) that viral hepatitis can give rise to lesions in the liver of the type found in our Case 2. The clinical history of our Case 2 was almost identical with that of our Case 1 who actually had giant-cell hepatitis. Familial occurrence of giant-cell hepatitis is well known (2, 4, 25, 29, 48). Lastly the following features, typical for congenital malformation of the intrahepatic bile ducts, were absent in our Case 2.

Congenital atresia of the intrahepatic bile ducts is most commonly associated with maldevelopment also of the extrahepatic biliary tract (1). Only 10 cases have been published with isolated intrahepatic bile duct atresia (23). Even if it is usually looked upon as only partial (bile present in gallbladder and stools) (1), the percentage of bile ducts absent commonly lies close to 100 when quantitative assessments are made (1). The patients live in good health for years, although they have hyperlipemia, skin xanthomatosis, persistent jaundice, and secondary biliary cirrhosis (1, 23, 38). Jaundice appears early, usually on one of the first days after birth. It is slowly progressive and does not show periods of complete or almost complete disappearance (as the jaundice of giant-cell hepatitis often does).

Third sibling

Whether the intrauterine death of the third sibling also speaks in favour of the supposition that the mother is a healthy carrier of SH virus, is impossible to state. It is not definite that the supposed intrauterine strangulation by the cord was the actual cause of the death. There is no unanimous opinion about the incidence of abortions of stillbirths among mothers supposed to be carriers of SH virus (53). There are, however, some reports of families with cases of giant-cell hepatitis and subsequent stillbirths (13, 48).

Carcinome primaire du foie et hépatite à cellule géante chez le nourrisson

Exposé du cas d'une petite fille atteinte de jaunisse à l'âge de trois ou quatre semaines et chez laquelle à l'âge de 11 semaines une biopsie du foie permet de découvrir une hépatite à cellule géante. Elle se rétablit lentement toutefois la jaunisse ne disparut jamais totalement. Une biopsie du foie à l'âge de deux ans et neuf mois montra une guérison histologique avec des cellules parenchymales du foie normales, mais on trouva également des stases de bile et une légère fibrose portale. La patiente décéda à l'âge de

Summary

A report is given of a girl who got jaundice at 3-4 weeks of age and at 11 weeks was found by liver biopsy to have giant-cell hepatitis. She recovered slowly, although jaundice never disappeared completely. Liver biopsy at the age of 2 years and 9 months showed almost complete histologic restitution with normal liver parenchymal cells although some bile stasis and a slight portal fibrosis was found as well. Death occurred at 3 years and 7 months of age from pulmonary metastases from primary liver cell carcinoma superimposed upon a monolobular portal liver cirrhosis.

An elder brother died at about 8 months of age after an almost identical illness. Partial atresia (post-inflammatory or congenital) of the intrahepatic bile ducts was found at autopsy. A third sibling was stillborn.

The giant-cell hepatitis was tentatively supposed to be due to transplacental infection by serum hepatitis virus. The liver cell carcinoma was supposed to be related to the cirrhosis rather than to the giant-cell hepatitis *per se*.

trois ans et sept mois de métastases pulmonaires d'une cellule primaire cancéreuse du foie et d'une cirrhose monolobulaire portale du foie. Un frère aîné décéda à l'âge d'environ huit mois après une maladie presque identique. On trouva à l'autopsie une atresie partielle (post-inflammatoire ou congénitale) des canaux biliaires intra-hépatiques. Un troisième enfant fut mort-né. On suppose que l'hépatite à cellule géante est due à une infection transplacentale causée par le virus de l'hépatite. On présume que la cellule du carcinome du foie était apparentée à la cirrhose plutôt qu'à l'hépatite à cellule géante en soi.

Primäres Leberkarzinom und Riesenzellenhepatitis bei Kindern

Es wird über ein Mädchen berichtet, das im Alter von 3 bis 4 Wochen an Gelbsucht erkrankte, und bei der durch Biopsie im Alter von 11 Wochen eine Riesenzellenhepatitis festgestellt wurde. Das Kind erholte sich langsam, obwohl die Gelbsucht nie ganz abklang. Eine weitere Leberbiopsie im Alter von 2 Jahren und 9 Monaten zeigte eine fast vollständige histologische Wiederherstellung mit normalen Leberparenchymzellen, obwohl auch eine gewisse Gallenstauung und eine leichte portale Fibrose gefunden wurden. Der Tod trat mit 3 Jahren und 7 Monaten ein, und zwar auf Grund einer Lungenmetastase des primären Leberzellenkarzinoms, das eine monolobuläre Leberportenzirrhose überlagerte. Ein älterer Bruder starb nach einer fast identischen Krankheit im Alter von ungefähr 8 Monaten. Bei der Autopsie fand sich eine partielle (postinflammatorische oder angeborene) Atresie der intrahepatischen Gallengänge. Ein weiteres Geschwisterkind wurde tot geboren. Von der Riesenzellenhepatitis wurde provisorisch angenommen, daß sie auf einer transplazentaren Infektion durch Serumhepatitisvirus beruhte. Das Leberzellenkarzinom hing vermutlich eher mit der Zirrhose als mit der Riesenzellenhepatitis an sich zusammen.

Carcinoma primario del hígado y hepatitis macrocelular en la infancia

Se presenta el historial de una niña que contrajo ictericia a las 3 ó 4 semanas de edad y en la que se halló, por biopsia a las 11 semanas, que sufría de hepatitis macrocelular. Se recuperó lentamente, aunque la ictericia nunca desapareció del todo. En la biopsia hepática a la edad de 2 años y 9 meses se vio una restauración histológica casi completa con células hepatoparenquimatosas normales, aunque se halló también cierta estasis biliar y una ligera fibrosis de la porta. La muerte sobrevino a los 3 años y 7 meses de edad a causa de una metástasis pulmonar del carcinoma primario de las células hepáticas, sobrepuesta a una cirrosis portal monolobular del hígado. Un hermano mayor murió a los 8 meses de edad después de una enfermedad casi idéntica. En la autopsia se encontró una atresia parcial (postinflamatoria o congénita) de los conductos biliares intrahepáticos. Un tercer hermano nació muerto. La hepatitis macrocelular se supuso, provisionalmente, que se debía a una infección transplacentaria por virus de hepatitis sérica. El carcinoma de las células hepáticas se supuso relacionado con la cirrosis más bien que con la hepatitis macrocelular en sí.

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BOOK REVIEW

Neurosekretion und Wasserhaushalt bei Neugeborenen und Säuglingen. Heinrich Rodeck.

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The inability of the newborn and young infant to excrete a concentrated urine is well established. This is partly due to a peripheral lack of response to adiuretin as has been shown by Heller, using the pitressin test, thus demonstrating a nephrogenic diabetes insipidus. An immaturity of the hypothalamic-neurohypophyseal system with a low endogenous production of adiuretin has also been postulated and supported by pharmacological experiments measuring the vaso-pressin and oxytocin activity of extracts from the neurohypophysis of various species at different ages. The author has attacked this problem with a histochemical technique using Gomori's method for the staining of the neurosecretory cells, which was first introduced by Bargmann. The amount of granules in the paraventricular and supra-optic nuclei and in the neurohypophysis together with the tracts connecting these centers makes a certain quantitative estimation of the neurosecretory activity possible. This was found to be absent in several newborn animals and present to a very small degree in human fetuses and newborns as compared to older children and adults. From this it is concluded that the immaturity of the hypothalamic centers and the neurohypophysis may be partly responsible for the deficient homeostatic mechanism, regulating the water-salt balance of the newborn. Other peculiarities of water balance in the young infant are also reviewed. The various conceptions concerning the location of primary formation of the neurosecretory product are also discussed as is the question of the

possible identity between this product and adiuretin. The monograph, well illustrated with microphotographs, seems well worth the Moro-prize, which it was awarded in 1957.

B. Hellström, Stockholm

Wewetzer, K.-H.: Das Hirngeschädigte Kind. Psychologie und Diagnostik.

117 s. Thieme, Stuttgart 1959. Pris. DM 19.80.

During the earliest period in the development of child psychiatry the psychodynamic approach was predominant. During recent years, however, a somato-psychological approach has come more and more to the fore. Mental disturbances based on (primarily due to) cerebral lesions have been devoted especial attention; and in particular the slight injuries that result in certain disturbances of perception, train of thought, rate of reaction, etc. have proved to be important. These states are diagnosed with difficulty, however. Attempts have been made to demonstrate these disturbances of function by means of special psychological tests. Of fundamental importance in this field are Goldstein and Scheerer's book *Abstract and Concrete Behaviour* (1941), Strauss and Lehtinen's book *The Brain-injured Child* (1947) and its continuation by Strauss and Kephart (1955). Wewetzer acknowledges the theories put forward by these authors, and describes in this work an investigation on a group of children with brain injury, which are compared with an equal-sized group of healthy controls similar with regard to age and intelligence quotient. All children were examined by 8 different tests that theoretically could be expected to give different results in the two groups. He describes the technique, and valuable observations made during the testing. The results are treated

statistically from different points of view. The investigation has shown that certain of the tests give in most cases very much worse results among children with brain injury, irrespective of the level of intelligence, and that they are therefore useful both for purposes of differential diagnosis and to elucidate certain particular disabilities, for example

such concerned with reading and writing, that these children may have. The investigation has been carried out on a strict scientific basis, and is clearly set out. It is of the greatest value to the child-psychiatrist, both from the theoretical point of view, and with regard to the practical advice it contains.

A.-L. Annell, Uppsala

ANNOUNCEMENT

The Guigoz and the Nestlé fellowships

The fellowships of research on nutrition founded by the Guigoz Works and by the French Nestlé Company will be awarded in the Spring 1960. The candidates are requested to send the following papers to the International Children's Centre, Château de Longchamp, Bois de Boulogne, PARIS XVI^e:

a)—a *Curriculum Vitae* mentioning their work on biological and social problems concerning feeding or nutrition of infants and children,

b)—a *letter of introduction* by one of their masters,

c)—a *description of the studies* which they wish to pursue.

The candidates must have an adequate command of the French language.

At the end of their fellowship, the fellow or fellows will be expected to remit to the International Children's Centre a scientific paper on the subject which they will have studied during the year of their fellowship.

From the Neonatal Department of the 1st Municipal Hospital of Brno (Head: Anna PojEROVÁ, M. D.) and the 3rd Internal Clinic of Masaryk University (Head: Professor Jaroslav Pojer, M. D., Ph. D.), Brno, Czechoslovakia

Ceruloplasmin in Early Childhood

by ANNA POJEROVÁ and JOSEF TOVÁREK

Ceruloplasmin was isolated for the first time by Holmberg & Laurell in 1948 from human plasma and the plasma of swine. It is an alpha 2 globulin containing approximately 0.32 per cent copper which gives it a bluish tint. Out of the total plasma-proteins it forms 0.03 per cent. Its molecular weight is 150,000. It contains 96 per cent of the total content of plasma-copper. The remaining 4 per cent of the copper is loosely bound with plasma-albumin (1, 9), which probably transports this metal (6).

Under normal conditions in the healthy person only a very small amount of copper is absorbed daily (6) and this disappears from the plasma very rapidly (6). Ceruloplasmin is an enzyme, being the oxidase of blood-plasma. It oxydizes a number of substrates such as benzidine, paraphenylen-diamine etc. On this property and on an antigenic property (by the immunisation of rabbits with human ceruloplasmin we obtain Anti-Human-Ceruloplasminserum) rest methods for the estimation of the amount of ceruloplasmin in the serum (1). A healthy person has approximately 34 mg of ceruloplasmin per 100 ml of plasma or of serum (9). A smaller amount of this enzyme is contained in the liver and in the kidneys. The central nervous system, the spleen, bile and erythrocytes do not contain ceruloplasmin (1). A raised amount of ceruloplasmin in the serum has been found in

infectious diseases (tuberculosis, pneumonia and others (7)), in infarction of the myocardium (2), in 70–89 per cent of all psychic diseases (1) and in pregnant women (2, 9, 15, 16). A low value of ceruloplasmin has been found in hepatolenticular degeneration (1), in severe liver damage accompanied by hypoproteinemia (19) and in the fetus (15, 16). In this group a decreased ability in the synthetisis of the apoferment of ceruloplasmin is presupposed (1, 19). The lowered values of ceruloplasmin in the nephrotic syndrome are explained by its loss in the urine (9).

We made it our task to examine the level of this enzyme, in the serum of the newborn and of older infants, and to ascertain the age at which ceruloplasmin reaches the characteristic level of adults. At the same time we examined the values in the serum of the cord, in women towards the end of pregnancy, in women during delivery and in women after delivery. As a normal level we used the results obtained by an examination of ceruloplasmin in the serum of 46 healthy blood donors before the first taking of blood.

Method

Ceruloplasmin was determined spectrophotometrically according to Ravin (12). As substrate the salt of paraphenylen-diamine

TABLE 1. *Values of ceruloplasmin in the serum of the newborn from the 1st to the 18th day of life. (Ceruloplasmin is given in extinction values multiplied by 1000 — according to Ravin's method.)*

Age in days (the 1st day = 0,01–24 hrs)	1	2	3	4	5	6	7	9	14	17	18
Number of samples	7	8	7	7	7	7	5	1	1	1	1
Range	65–180	120–400	120–350	60–350	90–320	120–460	125–340	290	130	140	210
μ	137.85	243.12	197.14	228.57	169.28	223.57	217.00				

hydrochloride was used. Its value is expressed by the coefficient of extinction multiplied by 1000. The determination was done using the spectrophotometer Koutský K_{560} at a transparency of 530 m μ .

Material and Results

The value of ceruloplasmin was measured in the serum of healthy adults, of cord blood (both arterial and venous, taken from the placental stump of the cord immediately after the separation of the child by free flow without pressing the cord), of the newborn and infants from the 1st to the 15th month of age, of pregnant women, of women during delivery and of women after delivery. All the children from whom we took blood samples were healthy. The newborn infants were mature and varied in birth weight from 2350 g to 4750 g. Likewise all the women examined were healthy. Pregnancy, delivery and the puerperium were without complications. Both children and women were chosen at random. We used no samples of blood altered by the slightest trace of hemolysis.

The results of the examinations are shown in tables and figures. Table 1 includes the values of ceruloplasmin in the serum of newborn infants from the 1st to the 18th day of life, Table 2 records the values in children from the 1st to the 15th months of life; Table 3 shows all the determined values of ceruloplasmin: in women before, during and after delivery, in fetal serum, in children from birth till the end of the 1st year of life, and in normal human subjects. In Fig. 1 are shown 15 children in whom it was possible to determine the values of ceruloplasmin twice during the 1st week of life. Mostly they show a rise, exceptionally a fall. In Fig. 2 are to be seen the values in cord serum and the rise in values in the 1st year of life in quarter's concentrations in comparison with normal values. In Fig. 3 are expressed the values found in pregnant women, in women at delivery, and in women in the early puerperal period as

TABLE 2. *Values of ceruloplasmin in the blood serum of infants from the 1st to the 15th month of life. (Ceruloplasmin is given in extinction values multiplied by 1000 — according to Ravin's method.)*

Months	1	2	3	4	5	7	8	9	10	11	12	13	15
Number of samples	52	4	7	3	7	1	1	3	5	4	2	1	2
Range	60–460	220–410	180–430	240–340	120–400	400–290	130–460	360–550	160–420	380–410	440–400		200–400
μ	206.16	340	335	280	246			300	430	345	395		360

TABLE 3. *Values of the ceruloplasmin:*

	μ	δ	δ_{μ}	Range
In 20 pregnant women from the 29th day to 10.30 hrs before delivery ^{a,b}	676	± 48	± 10.75	570-750
In 15 women during delivery	646	± 70.8	± 18.25	410-750
In 42 mothers from the 11th hr till the 12th day after delivery	638.5	± 96.2	± 14.8	340-820
In 32 samples of cord serum	207.5	± 83	± 14.7	80-380
In 52 newborns from the age of 2.40 hrs till the 18th day of life	206.16	± 91.5	± 12.7	60-460
In 63 children in the first quarter of life	228.4	± 100.8	± 12.65	60-460
In 10 children in the second quarter of life	262	± 87.6	± 27.7	120-400
In 5 children in the third quarter of life	322	± 116.5	± 52	130-460
In 11 children in the fourth quarter of life	400.9	± 86	± 25.9	160-550
In 46 healthy normal adults	414.35	± 74	± 10.9	230-600

^a 1st day = 0,01 hr till 24 hrs of age etc.

^b In all 21 samples were examined, but the value of 220 found on the 4th day before delivery, the closest following value being 570, was not taken into account because of its peculiar low value, the cause of which remained unexplained.

Ceruloplasmin is given in extinction values multiplied by 1000 according to Ravin's method.

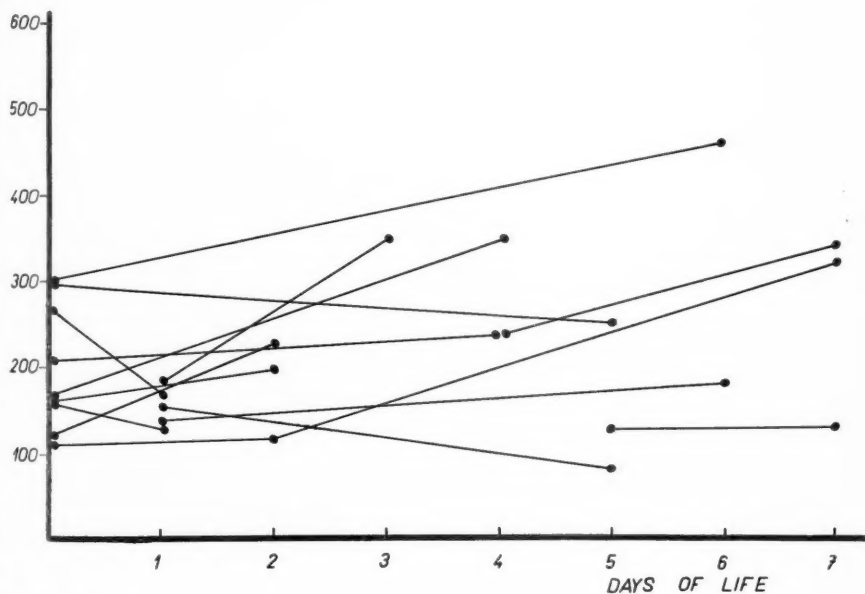


Fig 1. The values of ceruloplasmin, taken from 15 children twice during the first week of life. A connecting line is drawn between specimens taken from one and the same child. Ceruloplasmin is given in extinction values multiplied by 1000 (according to Ravin's method).

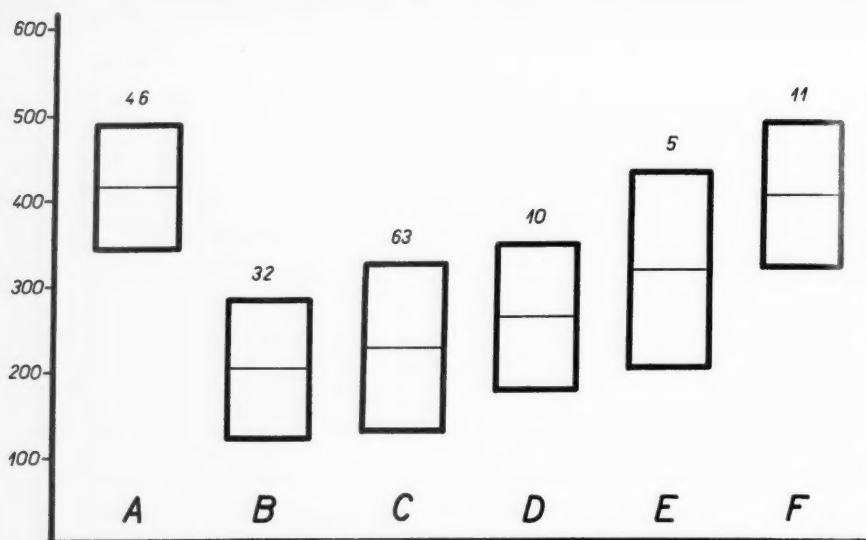


Fig. 2. The values of ceruloplasmin (A) in serum of normal human subjects (46 specimens), (B) in cord serum (32 specimens) and in serum of children in the first year of life concentrated into three month groups (C—the first quarter, 63 specimens, D—the second quarter, 10 specimens, E—the third quarter, 5 specimens, F—the fourth quarter, 11 specimens). Ceruloplasmin is given in extinction values multiplied by 1000 (according to Ravin's method.)

opposed to values in cord serum and in the serum of children from birth to the 18th day of life. The slightly dotted stripe in the centre shows normal values.

The blood from women before, during, and after delivery, was taken at the Obstetrical Department of the 1st Municipal Hospital in Brno.

Discussion

Scheinberg *et al.*, who examined ceruloplasmin by the method of Holmberg & Laurell in 12 samples from the blood of mothers just before delivery and in 12 samples of cord serum from their children, found the values of ceruloplasmin in the maternal plasma to be 55.56 mg in 100 ml. In the cord plasma they found a value of 6.5 mg in 100 ml. In 15 couples (mother and child) they measured copper bound to albumin (not bound in ceruloplasmin) and

found values slightly raised in comparison with normal values. These values, however, were not significantly different from those found in the cord serum (16).

Markowitz *et al.* using the immunological method (9) found 84 mg of ceruloplasmin per 100 ml of serum in 10 pregnant women in the last three months of pregnancy.

Sala & Gambara measured ceruloplasmin in the serum of 8 couples (mother and child) according to Ravin's method and found a value of 0.395 (E-530) in maternal serum and 0.075 (E-530) in cord serum.

High values of ceruloplasmin in pregnant women were also found by Adelstein (2).

Besides other values all the mentioned authors also measured the total copper in the plasma and found a clear correlation between the values of total copper and those of ceruloplasmin. From this it is clear that hypercupremia in pregnancy and hypocupremia in the fetus is caused by a rise or fall of ceruloplasmin in the serum (2, 9, 15, 16).

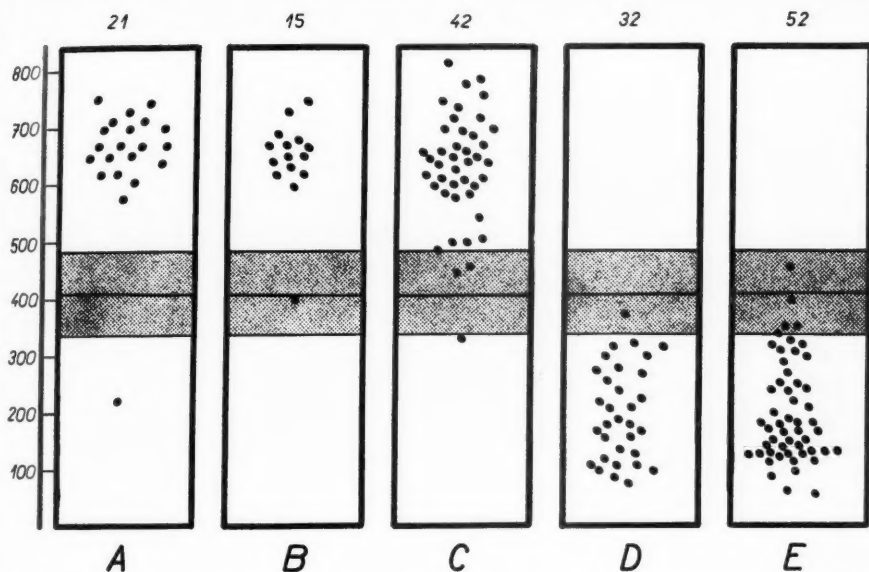


Fig. 3. The values of ceruloplasmin in serum (A) of women towards the end of pregnancy (21 specimens), (B) of women at delivery (15 specimens) and (C) of women in the early puerperal period (42 specimens) as opposed to values (D) in cord serum (32 specimens) and (E) in the serum of children from birth to the 18th day of life (52 specimens). The slightly dotted stripe in the centre shows the normal values. Ceruloplasmin is given in extinction values multiplied by 1000 (according to Ravin's method).

From our measurements it is evident that the value of ceruloplasmin in the serum of cord blood is about half of the value of ceruloplasmin in the serum of normal human subjects and roughly only a third of the value in women at the end of pregnancy. The serum values in children did not change in the 1st month of life in comparison with the values in cord serum; in the third quarter (i.e. the third three month period) however, they rose by about half, and only in the fourth quarter did they equal the values in normal adults. In the serum of our pregnant women the values were half again as high as in normal adults. In the first few days after delivery they showed

a small but decided fall. The difference in our values of the cord serum as opposed to the values of the maternal serum was not so great as the difference recorded by Scheinberg & Sala (15, 16) in their cases. The relation between the value of ceruloplasmin in maternal plasma and the normal value, as it has been given by Scheinberg (16), is the same as the corresponding relation established in our determinations.

The values found in the newborn showed no dependence upon the weight and the length of the child. Neither are they dependent on the duration of intrauterine life as far as the date of the last menstruation or the date of conception could be determined. Nor was any dependence

upon sex or the level of bilirubin in the serum proved.

Scheinberg *et al.* think that ceruloplasmin does not diffuse through the placenta because of the size of its molecule. In consequence, no balance can take place between the maternal and fetal blood (16). The low value of ceruloplasmin in fetal blood is probably not caused by the insufficiency of copper in fetal life (15) (copper not bound as ceruloplasmin very likely diffuses freely through the placenta (16)), but seems to be the result of the lowered ability of a functionally and morphologically immature liver (13, 17), to synthesize the apoferritin of ceruloplasmin (19).

Cartwright considers ceruloplasmin as the probable regulator of the resorption of copper from the intestines (5). Abderhalden says that this is also borne out by the observation that the blood of the newborn contains perhaps only 12 per cent of that amount of ceruloplasmin, which is present in his mother's serum (1). It has been shown that the level of ceruloplasmin in the serum slowly rises from birth to the 1st year of life. The moment of birth changes the child's way of nourishment; the blood route is replaced by the peroral route, the child begins to take in copper with colostrum and his mother's milk and to a relatively high degree. In Axtrup's view there is no need to fear a copper deficiency in infants (3). If in the first week of life the infant receives 500 ml of mother's milk daily, it takes in about $\frac{1}{4}$ mg of copper a day (10), which comprises $\frac{1}{8}$ of the daily need of an adult (7). At about the age of six months the child begins to receive a mixed diet. Thus in quality his diet slowly approaches that of an adult,

which in normal circumstances, i.e. if provided in sufficient quantity, easily satisfies the daily need of copper in an adult (7). Similarly as with quantity the formation of individual enzymes is regulated by the requirement of the organism (13), we may perhaps suppose that the synthesis of ceruloplasmin is effected after the maturation of the liver, caused by the increasing need of the organism to regulate the resorption of copper from the intestines.

It has been shown that orally administered radioactive copper can be recovered in the faeces of control subjects in a larger proportion than in those of patients with hepatolenticular degeneration (4). The increased absorption of copper and the accumulation of copper in some organs of patients with Wilson's disease is the hypothetic consequence of congenital deficiency in the formation of ceruloplasmin, i.e. of the hypothetic regulator of copper resorption from intestines (5).

It is well known from the literature, that within the period extending from birth to the end of the first year the level of alpha globulin in the blood shows a gradual rise (8, 11, 18). Alpha 2 globulin rises from 6.8 per cent of the total serum protein in the newborn to 10.0 per cent in the infant (no exact statement in regard to age is given) (11).

It is interesting that this relation is also shown by our values of ceruloplasmin: about the age of six months the level of ceruloplasmin rises by 50 per cent and about the age of twelve months by approximately 100 per cent.

The high values of ceruloplasmin in pregnancy have so far not been explained. It is probable that the rise depends upon hormonal balance characteristic for this state. A diminished level of hypercupremia was shown by administration of ACTH to

leukemic patients (2). In all Rovello's cases of hyperthyreotic women hypercupremia was ascertained; after suitable treatment they showed normal values (14).

Summary

Determination of the level of ceruloplasmin in the serum of the newborn and infants was performed. It is shown that ceruloplasmin reaches the level of adults ($\mu = 414.35$) only at the end of the 1st year. The level of ceruloplasmin in the

cord serum ($\mu = 207.5$) is about half of the level of ceruloplasmin in the serum of normal human subjects. In the 1st month of life it does not differ from the values of cord serum. In the third quarter (i.e. the third three month period), however, it rises by half and only the fourth quarter values approximate the values of adults.

In the serum of women before, during and after delivery the values of ceruloplasmin were half again as high as in normal adults (676, 646, 638.5 respectively).

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Harvard Medical School, Boston

Water and Electrolyte Economy in Newborn Infants of Diabetic Mothers

by CHARLES D. COOK, DONOUGH O'BRIEN¹, JOHN D. L. HANSEN²,
MARC BEEM and CLEMENT A. SMITH

The excessive size and weight and the increased mortality of infants born to diabetic mothers continue as puzzles for obstetricians and pediatricians (2-4). In an attempt to reveal some abnormality of body components at birth, water, electrolyte and nitrogen balances were measured in such infants during the period of postnatal adjustment. This report presents the results of studies carried out during the first three days of life on 19 diabetic mothers' infants and compares them with previously reported similar observations on normal control infants (5).

Material and Methods

The severity of the maternal diabetes was graded according to the Joslin Clinic classification (17) and ranged from the mildest (A) to the most severe (F). Fifty-eight per cent of the mothers were in the more severe categories, C to F. The gestational ages ranged from 33 to 37 weeks, but all but two were between 35 and 36 weeks. Thirteen of the infants were in an atmosphere supersaturated with water for two or more days.

The investigation was supported by grants from Lederle Company, M. & R. Laboratories, and the Association for the Aid of Crippled Children.

Presented in part to the American Pediatric Society, Buck Hill Falls, Pennsylvania, May 1954.

¹ Grocer's Company Research Scholar.

² Cecil John Adams Memorial Travelling Fellow.

The only feedings during the period of observation were glucose water begun on the first day of life in two infants, on the second day in three and on the third or fourth in the other 14. It appears from the work of Hansen & Smith (5) that electrolyte and nitrogen excretion are probably not influenced by water or glucose intake during the first three postnatal days so that all 19 infants were considered comparable to the normal controls in respect to the excretion of these substances. However, since weight loss and urine output are influenced by ingested and atmospheric water (5, 9), weight changes and urine measurements were used in only 13 of the infants for the first two days of life for comparison with the controls. All of the infants had uneventful postnatal courses without evidence of respiratory distress or other abnormality.

Because of the need for accurate urine collections only males were studied. Collections were ended at the voiding closest to 24, 48, and 72 hours of life. The urine was analyzed for sodium and potassium (16), chloride (15), and nitrogen (11).

Results

The birth weights and lengths of the diabetic mothers' infants plotted against gestational age and compared to values for normal infants (13) are shown in Fig. 1. The diabetic mothers' infants were, with two exceptions, above average normal

**BIRTH WEIGHT AND LENGTH
OF
DIABETIC MOTHERS' INFANTS**
(NORMAL CURVES FROM SCAMMON AND CALKINS)

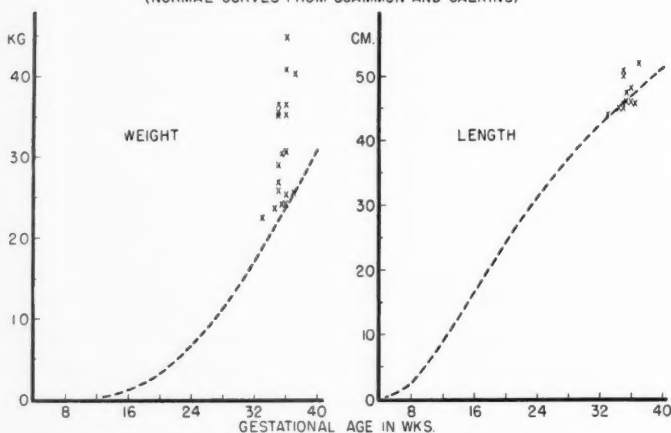


Fig. 1. Birth weight of 19 and length of 12 infants of diabetic mothers. x = diabetic mothers' infants. --- line represents average curve from data of Scammon & Calkins (13).

RENAL SODIUM EXCRETION
(TOTAL FOR FIRST 3 DAYS)

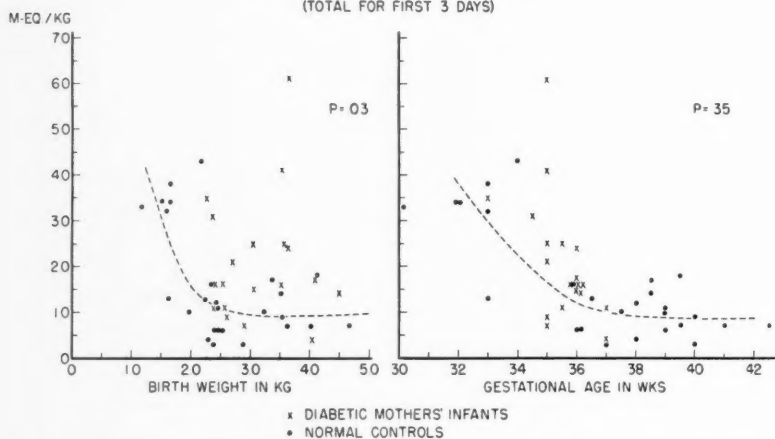


Fig. 2. Renal sodium excretion for 19 infants of diabetic mothers. --- line represents average values for normal infants (5).

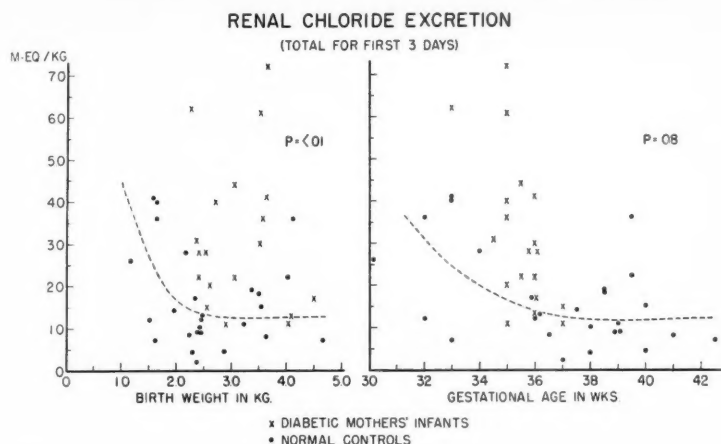


Fig. 3. Renal chloride excretion for 19 infants of diabetic mothers. --- line represents average values for normal infants (5).

weight for their gestational age and in many cases were strikingly so. Their lengths averaged only about 1 cm more than the expected normal.

The total urinary excretion of sodium in mEq/kg of birth weight during the first three days of life charted in relation to birth weight and gestational age is shown in Fig. 2. The infants of diabetic mothers as a group excreted significantly more sodium than the controls ($p = .03$) when compared on the basis of birth weight. When the comparison was made on the basis of gestational age, however, the difference, though suggestive, was not significant.

In the case of urinary chloride excretion (Fig. 3) the increase in the output of the diabetic mothers' infants was, in relation to birth weight, more pronounced, but again was not significantly different from normal when compared on the basis of gestational age. The excretion of potassium (Fig. 4) showed the same relation to

birth weight and gestational age as did sodium and chloride. In regard to nitrogen excretion, no differences between the infants of diabetic mothers and the controls could be shown for either basis of comparison. Serum chloride estimations were made shortly after birth and on the third day in 10 of the diabetic mothers' infants and were consistently within the normal range (98 to 111 mEq/L).

The weight losses and urine volumes (both expressed per kg of birth weight) for the first two days in the 13 diabetic mothers' infants treated uniformly in respect to water intake (i.e. none except supersaturated environmental atmosphere) are shown in Fig. 5. Both were greater than found for the control group of infants (5) but this difference is particularly striking for weight loss as high humidity has been shown to decrease weight loss in normal infants.

None of the findings could be correlated with the severity of the maternal diabetes.

RENAL POTASSIUM EXCRETION

(TOTAL FOR FIRST 3 DAYS)

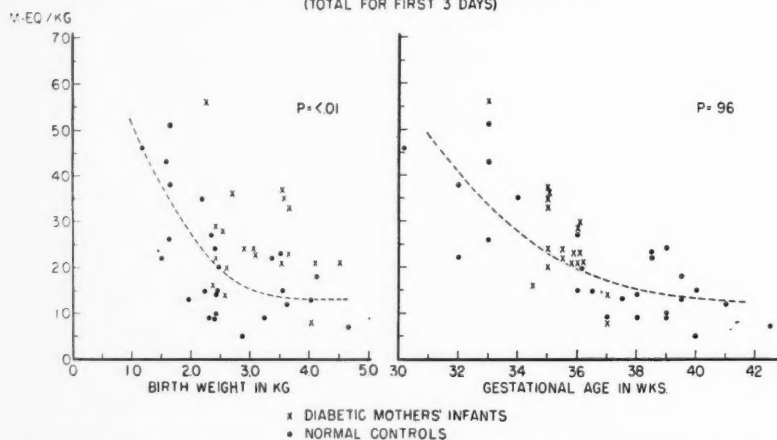


Fig. 4. Renal potassium excretion for 19 infants of diabetic mothers. --- line represents average values for normal infants (5).

WEIGHT LOSS COMPARED TO URINE VOLUME

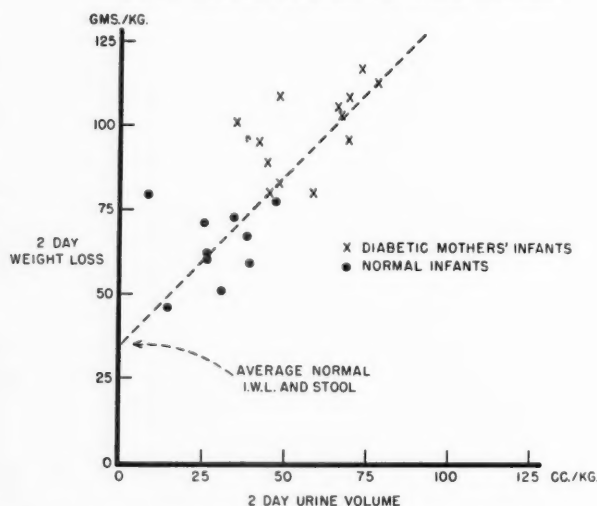


Fig. 5. Weight loss and urine output for 13 infants of diabetic mothers compared to values for normal infants. Thirty-five g/kg is the average 2 day insensible weight and stool loss for normal infants (5) of approximately the same gestational age as the diabetic mothers' infants.

TABLE 1. *Comparison of data from four diabetic mothers' infants.*

Case No.	Gest. age wks	B. wt. kg	2 day wt. loss g/kg	2 day urine vol. cc/kg	2 day electrolyte loss mEq/kg		
					Na ⁺	Cl ⁻	K ⁺
2	35	3.57	106	66	1.5	2.7	2.6
17	35	3.53	113	78	2.2	3.9	2.7
5	35	2.70	96	69	1.4	2.9	2.5
16	34 ¹ / ₂	2.37	103	67	2.5	2.7	1.3

Discussion

The finding in the diabetic mothers' infants of a greater increase in birth weight than in length is consistent with previous reports (2, 3, 8, 10) and is not surprising since weight is the product of three dimensions of which length is but one. The excessive birth weight of these infants is accompanied by postnatal weight losses and urine and electrolyte outputs which suggest that there is an increased extracellular water retention in fetal life. The significantly increased excretion of potassium also suggests some loss of intracellular water, which, if present initially in excess, might not be accompanied by a proportionate nitrogen release. Possibly, this also reflects some intrusion of sodium into the cell at the expense of potassium. Comparisons with control infants of various birth weights and gestational ages further suggest that the diabetic mothers' infants are abnormal in body composition in relation to their birth weight but less abnormal in relation to gestational age. From this pattern of abnormality it would appear that the larger the fetus of the diabetic mother for its gestational age, the more probably would its adjustment to extra-uterine life involve a disproportionately great loss of urine water and electrolyte excretion. These findings and conclusions

are, in general, in agreement with those of Zetterström & Åberg (19) and Stapleton (14).

That these large water and electrolyte losses were not necessarily exhibited by all diabetic mothers' infants is shown in Table I which includes the data from four individual infants. Two of these infants were among the largest for their gestational age of 35 weeks; the other two were only slightly above the expected weight. The excess weight in the two larger infants is presumably due to an increased water retention. The fact that the weight losses and urine water and electrolyte losses were substantially the same in all four infants suggests that in the larger, and presumably more seriously affected infants, there is also some delay in the mechanisms by which the volume receptors make their postnatal readjustments. Such data suggest that fetal body composition cannot in an individual case be accurately inferred from the measurement of excretions during neonatal life and that more direct techniques, such as isotope dilution studies, are needed for the description of these infants. The data also suggest that other factors, in addition to a moderate excess of extracellular water, contribute to the excessive birth weight of the diabetic mothers' infants.

No definitive explanation for the excessive size of diabetic mothers' infants can result from the present data or from reported experimental work. Pedersen (10) has suggested that there is less overgrowth of the fetus if the maternal diabetes is well controlled and the maternal and fetal blood sugar levels are near the normal range rather than high. Exogenous insulin has been shown (12) to act like a growth hormone and it may be that the fetus of a poorly controlled diabetic mother may produce excessive amounts of insulin (7). Much experimental work has been done on the interrelation of growth hormone and insulin (1) and Young (18) has postulated that both the maternal diabetes and the large fetus may result from a slight but sustained over-secretion of pituitary growth hormone. Furthermore, Ikkos, Luft & Gemzell (6) have shown that human growth hormone administration is associated with retention of phosphorus, nitrogen, potassium, sodium and chloride. The work of Farquhar (2, 3) has suggested that excessive production of adrenal steroids may, at least in part, account for the excessive body water.

With the present material there was no opportunity to correlate fluid and electrolyte losses and respiratory distress. However, since the body composition of infants of diabetic mothers seems more consistent with their gestational age than with their size, it would seem logical to compare their morbidity and mortality to that of nondiabetic mothers' infants on the basis

of gestational age. If this is done, the differences in neonatal mortality rates decrease.

Summary

In spite of presently unexplained differences in water and electrolyte excretions and probable differences in body composition within the group of diabetic mothers' infants, the data presented suggest the following general conclusions. (1) Diabetic mothers' infants are usually considerably heavier and slightly longer than normal infants of comparable gestational age. (2) During the postnatal period of adjustment they excrete proportionately more sodium, chloride, and potassium than normal mothers' infants of comparable weight. Although they may excrete slightly more of these electrolytes than infants of comparable gestational age, nevertheless they resemble such premature infants in respect to electrolyte excretion. Thus, the increase in size is apparently not accompanied by an increased maturity in respect to body composition. (3) The increased urine outputs and weight losses of the diabetic mothers' infants suggest that these infants tend to have an excess body water at birth. (4) The individual variations and lack of consistent relationships between water and electrolyte excretion show that at least some infants of diabetic mothers have an impairment of postnatal volume receptor stimulus to contract their extracellular water.

Economie de l'eau et électrolyte chez les nourrissons nés de mères diabétiques

Les enfants de mères diabétiques sont d'ordinaire beaucoup plus lourds et un peu plus longs que les enfants normaux de même âge gestationnel. Pendant la période post-natale d'ajustement ils excrètent proportionnellement plus de sodium, de chlorure et de potassium que les enfants de mères normales d'un même poids. S'ils excrètent un peu plus de ces électrolytes que des enfants d'un même âge gestationnel ils sont cependant semblables à ces prématurés sous le rapport de l'excrétion électrolyte. Donc l'accroissement en taille n'est pas accompagné d'un accroissement de la maturité sous le rapport de la composition du corps. L'évacuation accrue d'urine et les pertes de poids de l'enfant d'une mère diabétique suggèrent que ces enfants ont tendance à avoir un excès d'eau dans le corps à la naissance. Les variations individuelles et l'absence de rapport entre l'excrétion d'eau et celle d'électrolytes montrent que certains enfants de mères diabétiques ont un défaut du stimulus récepteur de volume pour contracter leur eau extra-cellulaire.

Der Wasser- und Elektrolythaushalt bei neugeborenen Kindern diabetischer Mütter

Die Kinder diabetischer Mütter sind gewöhnlich beträchtlich schwerer und etwas länger als normale Kinder von vergleichbarem Gestationsalter. Während der postnatalen Anpassungsperiode scheiden sie verhältnismäßig mehr Natrium, Chlorid und Kalium aus als die Kinder normaler Mütter von vergleichbarem Gewicht. Wenn sie auch vielleicht mehr Elektrolyte ausscheiden als Kinder von vergleichbarem Gestationsalter, so gleichen sie doch den Frühgeburten im Hinblick auf die Elektrolytaus-

scheidung. So ist das Größenwachstum anscheinend nicht begleitet von einer zunehmenden Reife in Bezug auf die Körperzusammensetzung. Die erhöhte Urinausscheidung und die Gewichtsverluste der Kinder diabetischer Mütter lassen darauf schließen, daß diese Kinder eine Tendenz zu einem Überschuß an Körperwasser bei der Geburt haben. Die individuellen Abweichungen und das Fehlen beständiger Beziehungen zwischen der Wasser- und Elektrolytausscheidung zeigen, daß wenigstens einige Kinder diabetischer Mütter einen Fehler des postnatalen Volumenrezeptorreizes aufweisen, ihr extrazelluläres Wasser zurückzuhalten.

La economía hídrica y electrolítica en niños recién nacidos de madre diabética

Los niños de madre diabética son, por regla general, considerablemente más pesados y ligeramente más largos que los normales de edad gestacional comparable. Durante el período postnatal de ajuste, excretan proporcionalmente más sodio, cloruro y potasio que los niños, de peso comparable, de madre normal. Aunque pudieran excretar ligeramente más de tales electrolitos que niños de edad gestacional comparable, parecen niños prematuros en este aspecto. Así el crecimiento no va acompañado, aparentemente, por un aumento de madurez en la composición corporal. La expulsión incrementada de orina y las pérdidas de peso del niño de madre diabética sugieren que estos niños tienden a tener, al nacer, un exceso de agua corporal. Las variaciones individuales y la falta de relaciones constantes entre las excreciones de agua y electrolitos demuestran que al menos algunos niños de madre diabética sufren un defecto en el estímulo postnatal del receptor de volumen para retener su agua extracelular.

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Anaerobiosis in Normal and Asphyxiated Premature Newborns

by BOHUMÍR VEDRA and JIŘÍ ULRYCH

The relative acidosis in full term as well as in premature newborns is usually explained in terms of anaerobic metabolism (5, 7, 8, 9, 11, 16). In a previous paper (13) we have shown that the acid base balance of the full term newborn is closely correlated to the acidosis of the mother and that there is a close relationship between lactic acid in mother and child, the latter being lower. In this paper the relationship of lactic acid to premature deliveries has been studied.

Methods

Lactic acid was measured in maternal and fetal blood at the moment of birth. Blood from the antecubital vein of the mother was withdrawn at the moment when the newborn's head was delivered. Fetal blood was withdrawn from the cord as soon as it was available for manipulation. The same chemical and statistical methods were used as in the previous paper.

Results

In all, 30 mothers and their premature newborns up to the weight of 2500 g were followed. Of this group 18 were characterized by the pediatrician as normal premature newborns, 7 as asphyxiated

and 5 as hypotrophic. The problem of hypotrophy will be the subject of a future study, the group of hypotrophic newborns was therefore excluded.

Three problems were investigated: a) the interrelationship between the levels of lactic acid in mother and newborn, b) the relation between the degree of prematurity and the levels of lactic acid in the umbilical vein, c) the differences between lactic acid in normal and asphyxiated premature newborns.

a) *The relationship between lactic acid in the blood of the mother and the normal premature newborn*

TABLE I

	Number	Average (mg%)	S.D.
mother	18	32.8	3.4
umbilical vein	18	28.7	2.9
umbilical artery	17	30.0	2.5

The difference between the levels of lactic acid in mother's and umbilical vein blood of 4.1 mg % is highly significant ($p = < 0.01$). The difference between umbilical vein and artery blood of 1.3 mg % is not significant ($p = < 0.05$). The difference between the maternal and um-

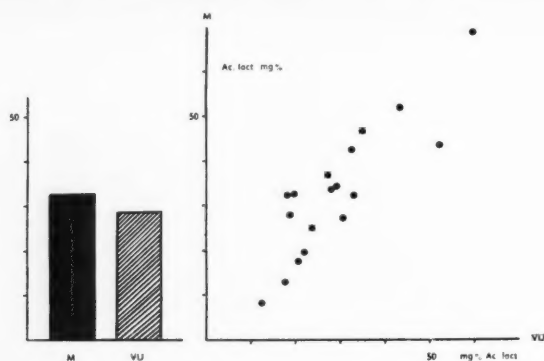


Fig. 1. The correlation between lactic acid concentrations in the mother (M) and the umbilical vein (VU).

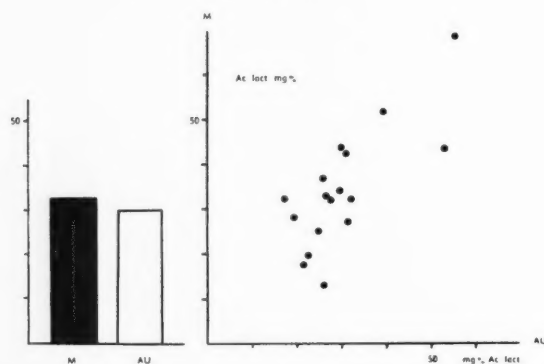


Fig. 2. The correlation between lactic acid concentrations in the mother (M) and the umbilical artery (AU).

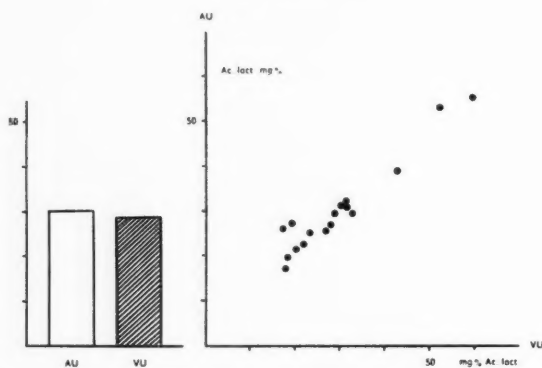


Fig. 3. The correlation between lactic acid concentrations in the umbilical vein (VU) and artery (AU).

bilical artery blood of 2.8 mg% is not significant ($p = < 0.05$).

The relationship between individual pairs of values are shown in Fig. 1 (mother and umbilical vein), Fig. 2 (mother and umbilical artery) and Fig. 3 (umbilical vein and artery).

The correlation coefficients are highly significant ($r_1 = 0.87$, $r_2 = 0.76$, $r_3 = 0.96$).

b) *The relationship between the degree of prematurity and lactic acid in umbilical vein blood*

From Fig. 4 it can be seen that there is no correlation ($r = 0.15$) between the weight of the newborn and his umbilical vein blood lactic acid.

No correlation could be found as well between the menstrual age of the newborn and his lactic acid concentration.

c) *Lactic acid in asphyxiated premature newborns*

The number of asphyxiated newborns is too small, therefore we prefer to give the individual values instead of average values only.

From Table 2 it can be seen that there is no striking difference between the absolute values of lactic acid in asphyxi-

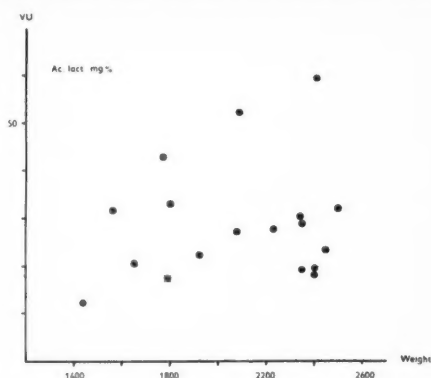


Fig. 4. The correlation between lactic acid concentration in the umbilical vein (VU) and the weight of the newborn

ated and normal premature newborns. All but one of the values in asphyxiated newborns are within the range of values for normal premature newborns.

The relationship of individual values between mother, umbilical vein and artery is not the same in all asphyxiated newborns: in Cases 415 and 1533, the values in umbilical blood are much higher than those in the mother, the umbilical artery values being higher than those in the umbilical vein. In one case (582) the umbilical artery value is as well much above that of the umbilical vein. These three results suggest a truly endogenous

TABLE 2.

No. of protoc.	Mother	Umbilical vein	Umbilical artery	Weight	Week of gestation	Note
415	60.4 mg%	71.2 mg%	73.3 mg%	1780 g	35	living
582	—	17.6	28.5	1760	30	living
3122	13.9	11.8	—	600	25	died after 4 h
1157	15.9	14.7	15.0	1700	32	died after 45 h
1533	14.1	32.6	36.4	830	26	died after 27 h
5840	25.4	27.0	—	950	26	died after 8 h
6060	—	32.7	—	290	20	died after 1 h

origin of lactic acid. In one case (1157) the differences are within the range of methodical error. From the results in the remaining cases we cannot draw any conclusions with regard to the origin of lactic acid. Nevertheless, the relatively low values of lactic acid in the cases of fatal asphyxia are noteworthy suggesting that anaerobiosis in the asphyxiated premature newborn did not play any significant role in protection against anoxia.

Discussion

Our results in premature newborns are in agreement with those in full term infants: there is the same correlation in both groups between lactic acid in mother and child. This close interrelationship can be explained only if we assume that it is the mother who influences the lactic acid levels in the fetus. As in full term so in premature newborns we can hardly imagine that a fetus of 1000–2000 g would be able, by means of its own lactic acid production, to influence the levels in a mother weighing 70–80 kg.

In discussing the problems of anaerobiosis in the human fetus it is necessary to define the conditions of anaerobiosis: 1) anaerobiosis as an adaptation to real hypoxia or anoxia. 2) "partial anaerobiosis" of the fetus in utero under conditions of so called "physiological" hypoxia.

The classical experiments of Himwich *et al.* (6) cited usually in connection with the theory of "partial anaerobiosis" fall rather into the first category of real anoxia. Newborn rats were submitted to nitrogen anoxia; they were thus asphyxiated. The equivalent conditions to

these experiments would be intrauterine asphyxia. There is no doubt that the human newborn or fetus is able to use anaerobic pathways of metabolism between the termination of O_2 supply and death (3, 14), i.e. in intrauterine asphyxia.

On the other hand, the newborns of Hendricks and Bell were normal, non asphyxiated. These newborns belong to the second category, i.e. so called "physiological hypoxia". There is little evidence that the physiologic conditions in utero are really hypoxic for the fetus (4). On the contrary, it has been proved that the O_2 consumption under normal intrauterine conditions is the same per kg weight/min as in the mother (Romney *et al.*), which suggests that the normal intrauterine conditions are not hypoxic. As Cross has shown, the younger the newborn, the less able it is to undertake anaerobic metabolism. The basic defence against hypoxia rests on a rapid decrease of O_2 consumption, not on the anaerobic breakdown of glucose.

We can look at this problem from another point of view: The acid base balance of the fetus has very small margins of safety (10). If the uneconomical anaerobic metabolism should bring any substantial energetic profit for the fetus, then the acid products would dangerously disturb its acid base balance.

Our results both in the normal non asphyxiated premature and in full term newborns suggest that the lactic acid in cord blood is not of endogenous origin, but rather of maternal origin. It does not mean that there is no fetal production of lactic acid in utero. We know that the fetus is able to produce lactic acid from the 7th week of gestation on (15).

Summary

The relationship of lactic acid levels in peripheral vein blood of the mother and umbilical vein and artery blood has been studied in premature normal and asphyxiated newborns. There exists a close relationship between the levels in the mother and fetus suggesting a high

degree of interaction. In view of the relative amounts of extracellular fluid of mother and fetus this relationship can be explained only on the basis of maternal production.

Some results from asphyxiated premature newborns suggest that anaerobiosis in the premature does not play a significant role in protection against anoxia.

Anaérobiose chez le prématuré normal et asphyxié

Le rapport entre les taux d'acide lactique dans le sang veineux périphérique de la mère, dans la veine ombilicale et le sang artériel fait l'objet d'une étude chez les nouveaux-nés prématurés normaux et asphyxiés. Il existe un rapport étroit entre ces niveaux chez la mère et le fœtus, ce rapport suggère une très grande interaction. La relation de quantité de liquide extracellulaire de la mère et du fœtus peut s'expliquer par la production maternelle. Quelques observations faites sur des prématurés asphyxiés permettraient de penser que l'anaérobiose chez les prématurés ne joue pas un rôle essentiel dans la protection contre l'anoxie.

Die Anaerobiose bei normalen und asphyktischen Frühgeburten

Die Beziehungen zwischen dem Milchsäure-Spiegel im peripheren Venenblut der Mutter und im Blut der Arteria und Vena umbilicalis sind an Hand von normalen und asphyktischen Frühgeburten untersucht worden. Zwischen diesen Spiegeln in der Mutter und im Fötus besteht in der Tat eine enge Beziehung, die auf einen hohen Grad wechselseitiger Beeinflussung

schließen läßt. In Bezug auf die Menge der extrazellulären Flüssigkeit der Mutter und des Fötus können diese Beziehungen auf Grund der mütterlichen Erzeugung erklärt werden. Gewisse Ergebnisse von Untersuchungen an asphyktischen Frühgeburten lassen darauf schließen, daß die Anaerobiose der prämaturnen Neugeborenen keine wesentliche Rolle hinsichtlich des Schutzes gegen die Anoxie spielt.

La anerobiosis en los recién nacidos prematuros normales y asfixiados

Habiéndose estudiado, en algunos recién nacidos prematuros normales y asfixiados, los niveles del ácido láctico en la sangre venosa periférica de la madre y en la sangre umbilical venosa y arterial, se ha visto que en efecto existe una relación estrecha entre los niveles materno y fetal, lo cual hace suponer un elevado grado de interacción. En cuanto a la cantidad del líquido extracelular, en la madre y el feto, tal relación puede ser explicada a partir de la producción materna. Ciertas conclusiones deducidas del estudio de recién nacidos prematuros asfixiados indican que la anerobiosis de los prematuros no desempeña un papel substancial en la protección contra la anoxia.

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Late Infantile Metachromatic Leucodystrophy of the Genetic Type

by BENGT HAGBERG, PATRICK SOURANDER, LARS SVENNERHOLM and HENRIK VOSS

Greenfield (1933) and Brain & Greenfield (1950) described six cases of late infantile metachromatic leucodystrophy, differing clinically and histologically from other known forms of so called diffuse cerebral sclerosis. The hitherto known cases have recently been reviewed in Britain by Jefferson (1958) and in the U.S.A. by Hain & LaVeck (1958). In the German literature this disease has been included as one of the subgroups of the familial diffuse brain sclerosis of Scholz, Bielschowsky & Henneberg (21). The purpose of this paper is 1) to present three cases of the late infantile type from the same family, two of them studied with clinical, pathological and chemical investigations of the CNS, and 2) to give facts supporting the thesis that these cases belong to a well defined disease entity within the group of cerebral sphingolipidosis, which are probably due to an inborn error of metabolism.

A. Clinical picture

Our three patients were all boys, two of them brothers and the third a second cou-

The expenses were partly defrayed by Expressen's foundation for prenatal research.

sin of the others. They belong to a large family (Fig. 1) from Jämtland in the mid western part of Sweden. Thorough investigation of the hereditary information concerning members of the family did not reveal any further similar cases, nor other relevant hereditary diseases.

CASE 1. *Roger O. Record no. U-a 922/57*

This boy was the youngest child in a family of 4. He had healthy parents and two healthy sisters. An older brother (Case 2) died at the age of 5 years. The patient was born at term; delivery was normal and the birth weight 4650 g. Somatic and mental development were normal during his first year. He walked at 12 months and talked at 2 years. The first symptoms appeared at the age of 15 months consisting of unsteady gait and slowly progressive weakness of the lower limbs, which were hypotonic; the tendon reflexes were normal. At 2½ years he was still able to walk with support, though with difficulty. In addition trembling movements of his hands were observed. His speech and mental development seemed unimpaired at this stage. During the following months successive deterioration with commencing muscular insufficiency and increasing tremor of his arms and hands developed. Stagnation or even regression of his mental development and slight retardation of his speech became obvious at the same time. When examined

in the Pediatric Clinic of Uppsala in 1957 at an age of three years he was severely handicapped, and only able to move himself slightly in bed on his arms and had a constant rattling type of breathing. He had no hypertonic fits. His mental development was that of about two years. He was kind and interested in what was happening in the ward. Neurologically his initial hypotonic diplegia had changed to marked hypertonic diplegia. In addition he was ataxic, especially in his upper limbs. The tendon reflexes could be elicited only with difficulty. The plantar responses were equivocal. The pupils reacted normally to light. The right optic disc appeared somewhat paler than the left but no other significant changes were seen. At otoneurological examination, central nystagmus was found. The cerebrospinal fluid contained 4 cells per ml and 110 mg of protein per 100 ml. Standard laboratory examination of the urine and blood were normal. His condition gradually deteriorated and soon he lay rigidly in bed with his legs extended and his feet in the equinovarus position. His arms were sometimes fully flexed, sometimes fully extended and pronated. He was unable to hold his head erect. He had frequent general hypertonic attacks with the body in the state of decerebrate rigidity. The tendon reflexes could no longer be elicited. Bulbar signs finally complicated the picture with swallowing and respiratory distress. Three months later he died of bronchopneumonia in the Children's Hospital, Östersund. The autopsy is reported below.

CASE 2. Kjell O. Record no. Ö-d. 326/52

He was the elder brother of Roger O., Case 1, and had also been a bright and healthy boy during his first year of life. He started to walk when 1½ years but never walked well. When he was less than 2 years his mother took him to the doctor because of his unsteady gait and weak feet. His legs were hypotonic with knock knees and valgus deformity feet. At 2¾ years he was much worse and unable to walk without

support. Obvious mental regression and deterioration of speech was observed. When nearly 3 years old his initial hypotonic insufficiency of the lower limbs had changed to hypertonic diplegia, which increased markedly during the next year. Exaggerated tendon reflexes, patellar clonus and spinal automatism were finally observed. His optic discs were somewhat pale without significant signs of atrophy. Otoneurological examination revealed undulating nystagmus of central type. An air encephalogram was normal. The electroencephalogram showed an increased number of slow frequencies. The cerebrospinal fluid showed less than 1 cell per ml. The protein was increased, Pandy ++ and Nonne +. The dye test and complement fixation test for toxoplasmosis were negative.

At four years he was severely mentally retarded and without any contact with the surrounding world. He could not sit up nor move in bed and had coarse rattling breathing. Three months later he died at home. Autopsy was not performed.

CASE 3. Kent E. Record no. Ö-d. 498/57

Somatic and mental development were normal during his first year. He started to crawl and to rise up on his legs but never learnt to walk which perhaps could partly be explained by bilateral subluxation of the hip joints. He was able to speak a few words before two years of age. When 2 years old his muscles were weak, hypotonic and hypotrophic, especially the legs. His tendon reflexes could not be elicited. He did not speak and seemed to be somewhat mentally retarded. In the cerebrospinal fluid 5 cells per ml were found; the protein was 75 mg per 100 ml. Aged 3 years he was much worse, being severely mentally retarded, and unable to sit or hold up his head. He could not talk. Neurologically he presented a picture resembling "chronic polyradiculitis" with marked flaccid tetraplegia, pronounced atrophy of muscles, and absence of tendon reflexes. The cerebrospinal fluid protein was

150 mg per 100 ml. He had also horizontal nystagmus of central type, slow-reacting pupils, peculiar hypertonic episodes, and athetoid movements, especially of his hands. In addition trophic disturbances of his skin and hypertrichosis were observed. Routine laboratory examinations of the blood and urine were within normal limits. No phenylpyruvic acid could be traced. The dye test and toxoplasma complement fixation tests were negative.

Aged 4 years his condition had deteriorated, he lay constantly on his back in distorted positions due to changing muscle tone. He was now more hyper- than hypotonic in his arms. His legs were extended and his feet were in an equinovarus position. He was quite helpless; feeding became increasingly difficult. Bulbar signs complicated the picture with difficulty in swallowing and rattling insufficient breathing. During his last days he was in a continuous hypertonic state. He died of bronchopneumonia. An autopsy was performed.

Clinical comments

Our three cases agree clinically with the original cases of Greenfield (17), Brain & Greenfield (9), and also with the description of other children with the same

disease (5, 10, 20, 23, 25). They are also similar to Belgian cases described earlier by van Bogaert & Scholz (7) which probably belong to the same group. The two sisters (family Ros) reported by these authors differ from the other cases in some respects, e.g. ataxic symptoms and signs were not observed; epileptic fits were a prominent feature, and the onset of the disease was noted first at an age of about three years, somewhat later than in our cases.

Summing up the clinical picture of this disease the first symptoms in most cases appear at 1-2 years of age, and are usually observed when the child starts to walk without support. At this first stage the gait is unsteady. The child has knock knees and valgus deformity of the feet. There is general hypotonia but no obvious paresis. Insidiously the child first loses the ability to walk or stand and finally to crawl. The hypotonicity may sometimes be so marked that myopathy may be suspected (17, 25, 26). The next stage is dominated by flaccid paraplegia or diplegia with diminished or absent tendon reflexes combined

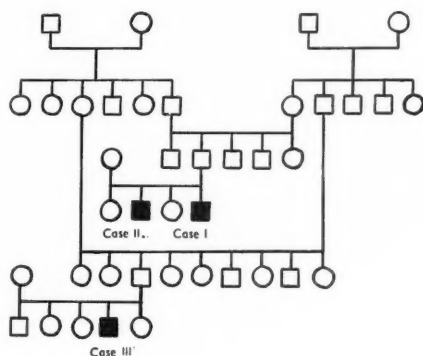


Fig. 1. The family tree of the three patients.

TABLE 1. *Summary of clinical data.*

	Case 1	Case 2	Case 3
Onset (age in years)	1½	1½-2	1½
Death (age in years)	3½	5½	4
Neurologic signs (at about 3 years)	hypertonic diplegia ataxia intention tremor central nystagmus pale disc right dysarthria "tonic fits"	hypertonic diplegia (ataxia?) central nystagmus pale discs (?) speech disorder	hypotonic tetraplegia athetoid movements central nystagmus slow pupillar. react. no speech at all "tonic fits" cerebral fever lost tendon reflexes
Protein in CSF	110 mg %	increased	150 mg %

with slight signs of pyramidal damage. A second variant is a pure spastic paraplegia with pronounced hypertonus but without signs of secondary motor neurone dysfunction. There is an early increase of the protein content of the cerebrospinal fluid. Spinal tumour, polyradiculitis and cerebral palsy are the main diagnostic errors at this stage. However, the neurological picture is soon complicated by ataxic signs with coarse tremor, nystagmus and speech disturbances, and approximately at the same time intellectual regression and apathy appear along with peculiar hypertonic fits, cerebral fever and sometimes optic atrophy. Most patients pass through a complex tetraplegic stage with variable muscle tone. During this stage pronounced hypertonicity of the legs may be combined with hypotonicity of the arms. The original dysarthria is converted to total aphasia. Finally bulbar symptoms complicate the picture with feeding and respiratory difficulties and the child usually dies when 3-6 years from secondary pulmonary infections. In this final stage generalized

decerebrate rigidity occurs. Cortical blindness and deafness may be added. The child no longer has any contact with his surroundings.

B. Post-mortem findings

Examination of the central nervous system

The brains and spinal cords from Cases 1 and 3 were fixed in 10 per cent formalin. Representative blocks were removed from the frontal, temporal and occipital lobes, pre- and post-central gyri, basal ganglia, amygdaloid complex and hippocampal region, mid-brain, cerebellum, pons, medulla oblongata, cervical and lumbosacral enlargements and the mid-thoracic level of the spinal cord, cauda equina, spinal roots and spinal ganglia. From these blocks paraffin sections of 10 μ were cut. They were examined histologically using the following staining methods: hematoxylin-eosin, hematoxylin-van Gieson, thionin, and the Weil-Weigert-Lillie method for myelin. Palmgren's silver technique was used for axons and Victorinblue for astrocytes. The Hotchkiss-Schiff periodic acid-fuchsin technique (PAS) was applied to both paraffin and frozen sections. Additional histochemical methods listed in Table 2 were applied to frozen sections 20 μ thick.

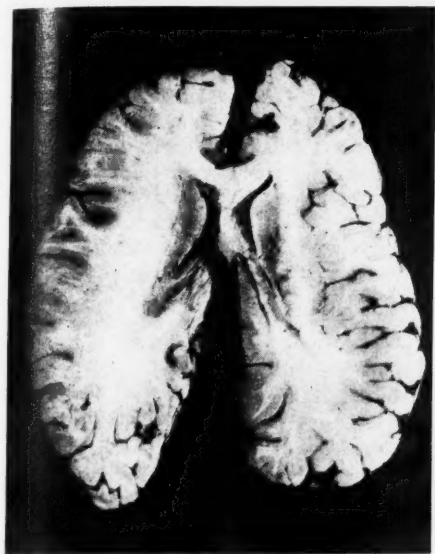


Fig. 2. (Case 1). Horizontal section through the brain after fixation. No obvious changes of the grey and white matter can be seen.

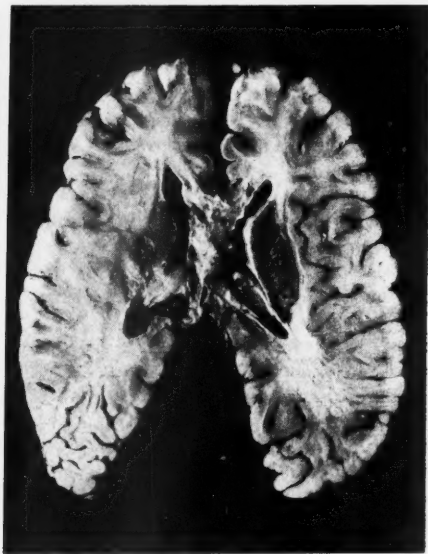


Fig. 3. (Case 3). Horizontal section through the hemispheres of the fixed brain. The white matter is reduced and slightly retracted from the cortex. Its cut surface appears somewhat rough and shows patchy grey discoloration particularly of the corpus callosum and the occipital lobes.

Case 1

Macroscopic findings (Fig. 2). After fixation the brain weighed 1200 g. It was normally convoluted. On section the white matter particularly in the occipital regions was slightly firmer than normal but without discoloration.

Microscopic examination. In all the regions examined the most prominent changes were seen in the white matter. The myelin sheaths showed intense degeneration and accumulation of large amounts of granular material had taken place. For the most part this material occurred as extracellular, round or oval shaped granular bodies, which stained well by various histological methods e.g. eosin and myelin stains. In sections stained by Scharlach R no bright red staining lipid was seen in the white or grey matter.

Cerebral cortex. The Palmgren silver technique did not reveal any changes in the cortex and most of the nerve cells appeared normal with ordinary thionin staining on paraffin sections. Using thionin and tartaric acid on frozen sections, purple coloured metachromatic deposits were found in the giant pyramidal cells of Betz. These deposits showed a strong positive PAS reaction. Similar metachromatic and PAS-positive deposits of fine granules were also present in occasional endothelial cells of capillaries, in some of the perineuronal satellites and microglial cells or free in the grey matter of basal cortical layers. In the same region a slight increase in fibrous astrocytes was noticed. Oligodendroglial nuclei were present apparently in normal numbers.

Cerebral white matter. The myelin staining in nearly all regions of both hemispheres was markedly reduced. Diffuse demyelination was most pronounced in dorsal parts of centrum semiovale. In high power magnification the remaining myelin sheaths showed varicosities and fragmentation. The axons were less affected than the myelin sheaths. However, in the severely damaged occipital areas only a small number of intact axons were seen. In frontal parts of the brain the axons were in general well preserved. Throughout the white matter and especially replacing the subcortical arcuate fibres large amounts of granular metachromatic and PAS-positive material was present. The optic radiations were not spared though somewhat lesser affected than other tracts. Most of the metachromatic substance was extracellular. In the demyelinated areas a moderate number of swollen "gemästete" astrocytes were present; some of them contained granular material in the peripheral parts of their cytoplasm. In areas with gross demyelination no oligodendroglial cells were present. Only very few phagocytes were recognized. In some places an accumulation of such cells with PAS-positive material was seen round the vessels.

Basal ganglia. Proliferation of astrocytes was prominent in the thalamic and lenticular nuclei. The large nerve cells in the medial pallidum and occasional neurones in the lateral thalamic nuclei contained PAS-positive granules. Such granules were also seen outside nerve cells in the paraventricular nucleus and in the amygdaloid complex. The internal capsule on both sides showed intense destruction of myelin and large amounts of voluminous granular bodies lying in rows parallel to the fibres.

The *optic tracts* stained rather weakly with ballooning of myelin sheaths and large amounts of granules. The axons were well preserved. There was moderate fibrillary astrogliosis. No oligodendroglial cells were found.

Cerebellum. Considerable loss of Purkinje cells had taken place. Many of the remaining

ones showed swellings of their axons. In the granular layer PAS-positive material was seen in occasional endothelial cells of capillaries and in phagocytes. The most striking changes were found in the white matter. Almost total demyelination with severe destruction of axons and a moderate excess of fibrillary astrocytes were present throughout. Everywhere metachromatic and PAS-positive granular bodies were abundant, the greatest number being concentrated just beneath the cortex and around the dentate nucleus. In frozen sections the neurones of this nucleus contained large collections of granular material staining metachromatically with thionin-tartaric acid. They also showed brown metachromasia with cresyl-violet and a PAS-positive reaction. No oligodendroglial cells were identified in the cerebellar white matter.

Brain-stem. In the mid-brain and pons the pyramidal tracts were demyelinated and numerous granular deposits were present. The loss of oligodendroglial nuclei was evident both in vertically and transversally coursing fibre systems. The latter fibres did not appear demyelinated. PAS-positive material was seen in nerve cells of the red nucleus and substantia nigra.

Medulla oblongata. Accumulations of granular bodies were seen in the severely demyelinated pyramids. Fine granules were seen in other fibre systems and in nerve cells of the inferior olivary and hypoglossal nuclei.

Spinal cord. Sections taken at various levels showed widespread degeneration of myelin sheaths especially of the lateral columns and the direct pyramidal tracts and to a lesser degree the posterior white columns. In the affected areas numerous small granular deposits were seen, most of them without nuclei but some of them inside phagocytic cells. Granular deposits were present also in the large motor nerve cells of the anterior horns. In the ventral and dorsal roots, particularly in those of the cauda

TABLE 2. *Histochemical reactions of the granular bodies.*

Methods	Chemical substances	Case 1	Case 3
Scharlach R.	neutral fats	—	—
Sudan black B.	neutral fats and phospholipids	+	+
Technique of Feigin (13)	cholesterol	—	—
Technique of Feigin (13)	cholesterol esters	+	+
Orcinol-sulphuric acid (13)	glycolipids (cerebrosides and gangliosides)	+	+
PAS reaction (29)	carbohydrates principally poly-	+++	+++
(Schiff-Hotchkiss)	saccharides and glycolipids		
PAS reaction after lipid extraction with chloroform-methanol (13)	mainly mucopolysaccharides	++	++
Alcian blue (13)	acid groups (acid glycolipids and mucopolysaccharides)	++	++
(Lison)			
Thionin-tartaric acid (16)	cerebroside-sulphuric acid and gangliosides = red metachromasia	+++	+++
(Feyrter's "enclosure" technique)			
Cresylviolet-acetic acid (13)	cerebroside-sulphuric acid and gangliosides = brown metachromasia	+++	+++
(v. Hirsch & Peiffer)			
Feulgen (29)	deoxyribonucleic acid	—	—

equina slight degeneration of myelin and numerous granules were found.

Case 3

Macroscopic findings. After fixation the brain weighed 1050 g. The convolutions of both hemispheres and especially the cerebellum showed marked atrophy. The left cerebral hemisphere appeared somewhat shrunken. On horizontal section the white matter particularly of the left centrum semiovale and the internal capsules was reduced and unduly firm. The white matter showed a patchy grey discoloration (Fig. 3). The changes were most pronounced in the occipital and cerebellar white matter. The ventricles were slightly dilated. The lower brainstem, both middle cerebellar peduncles and the pyramids appeared somewhat shrunken. The spinal cord and its roots showed no gross abnormality.

Microscopic examination. The histological changes in this case were qualitatively almost identical with those in Case 1 but were

much more intense. Points of divergence will be described.

Cerebral cortex. In silver impregnated sections, degenerated and fragmented axons were seen in basal parts of the precentral and occipital cortex corresponding to radiating demyelinated fibres. Metachromatic deposits were present not only in the giant pyramidal cells of Betz and their perineuronal satellites but also in occasional nerve and glial cells of the temporal cortex and in the deep layers of the occipital cortex. Moderately dense astrocytosis was found in these areas. As in Case 1 no loss of oligodendroglial nuclei was found in the cortex.

Cerebral white matter. In sections stained for myelin the white matter of the hemispheres including the internal and external capsules was more severely affected than in Case 1 (Fig. 4). This was true for the occipital lobes as well as for the frontal and temporal lobes. Throughout the demyelinated areas were scattered, irregularly beaded nerve fibres. In low power magnification the optic radiations stood out as more darkly stained

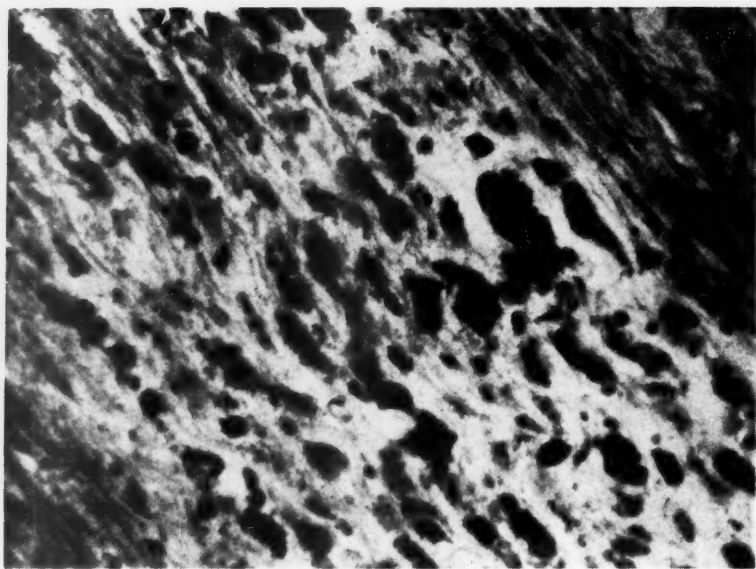


Fig. 4. (Case 3). White matter of the internal capsule showing degeneration of myelin sheaths and numerous free lying granular bodies staining dark with Weil-Weigert-Lillie method for myelin 350.

than the surrounding white matter. High power magnification revealed this to be due to dense accumulation of black staining granular bodies and a number of rather well preserved fine myelin sheaths. Throughout the white matter enormous numbers of apparently free lying granular bodies were present with the same staining properties as in Case 1. Frequent collections of granules were seen round the vessels. In places slight perivenous fibrosis and sparse infiltration with lymphocytes and occasional plasmocytes was noted. There was practically complete absence of oligodendroglial nuclei in the white matter of both hemispheres. Scharlach R stained frozen sections did not reveal any fat laden phagocytes. In most affected areas were many swollen-bodied astrocytes, some of them containing metachromatic and PAS-positive material at their margin. Fine fibrous gliosis was noted particularly in the occipital regions. Sections stained for axons

showed a definite loss of fibres and severe degeneration of many of the remaining ones. These changes were most pronounced in the occipital (Fig. 5) and precentral white matter and the internal capsules but were also present in the most frontal parts of the centrum semiovale. The phylo- and ontogenetically old mamillo-thalamic tract was rather well preserved.

Basal ganglia. The histological alterations in the lenticular and thalamic nuclei and amygdaloid complex were similar to those described in Case 1. The *optic tracts* showed numerous granular bodies. Their myelin sheaths stained poorly and widespread axonal degeneration was noted. Considerable astrogliosis was present. No oligodendroglial cells were detected.

Cerebellum. The number of Purkinje cells was markedly reduced. The axons of these cells were swollen. In the granular layer occa-

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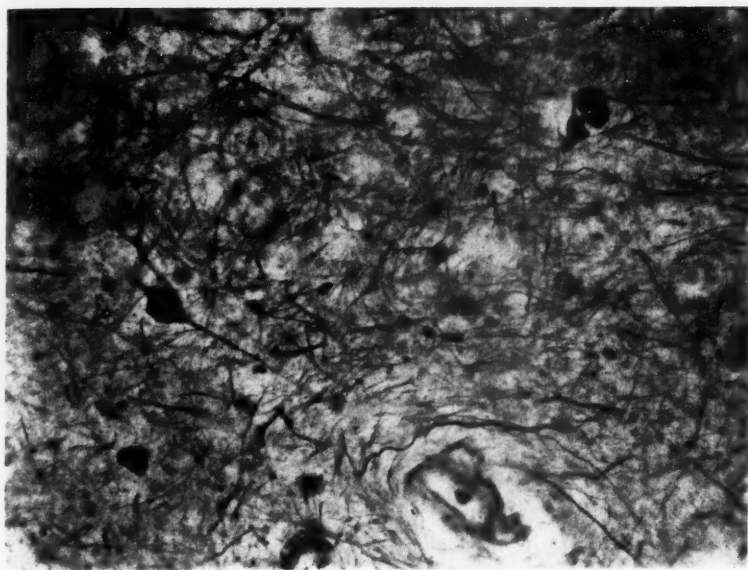


Fig. 5. (Case 3). White matter of the occipital lobe showing loss of axons and swelling and fragmentation of those which remain. Palmgren's silver technique $\times 350$.

sional phagocytes containing metachromatic granules were seen. Throughout the demyelinated white matter of the cerebellar hemispheres and vermis, granular bodies were found in great profusion. Destruction of axons was widespread and much more dense fibrillary gliosis than in Case 1 was present. No oligodendroglial nuclei or fat containing phagocytes of microglial origin were seen. Granular material which stained metachromatically was present in the nerve cells of the dentate nucleus (Figs. 6 & 7).

Brain-stem. The lesions were essentially the same as in the earlier case but in places more pronounced.

Medulla oblongata. Granules were present not only in the hypoglossal and inferior olivary nuclei but also in other nuclei, e.g. the motor and sensory nuclei of the trigeminal nerve. The pyramids were severely destroyed and showed numerous granular bodies.

Spinal cord. There was marked demyelination of both direct and indirect pyramidal tracts and elsewhere were many swollen myelin sheaths and abundant fine acidophilic granules. Clusters of similar material were seen in motor cells of the ventral horns. Only few oligodendroglial nuclei were detected in the white matter. In the ventral and dorsal roots granular bodies of varying size were much more frequent than in Case 1. As in Case 1 they were particularly abundant in the cauda equina but they were also present in the spinal ganglia.

Pathology of the viscera

CASE 1. Lung: microscopic examination revealed incipient bronchopneumonia. *Liver:* in the centrilobular zones a fine vacuolar degeneration was seen. In the periphery of the lobules there were numerous round metachromatic granules of varying size in the cytoplasm of many of the liver cells.

TABLE 3. *Metachromasia and PAS positive deposits in visceral organs of cases with metachromatic leukoencephalopathy.*

Investigation	Age in years	Metachromasia		PAS-positive deposits		Positive findings in other organs
		Liver	Kidney	Liver	Kidney	
Witte (1921)	42	liver cells	convoluted tubules, casts			metachromasia in anterior hypophysis and testis
Norman (1947)	18	walls of intrahepatic bile ducts	tubules and macrophages			metachromasia in macrophages of the gall bladder
Russel Brain & Greenfield (1950)	2 $\frac{3}{4}$	periportal histiocytes	looped tubules of Henle	liver cells, histiocytes, Kupffer cells	free margin of the convoluted tubules, a few casts	
	2 $\frac{1}{4}$	periportal histiocytes	looped tubules of Henle			
Bertrand, Thieffry & Bargeton (1954)	2 $\frac{1}{2}$			Kupffer cells		PAS positive material in RES cells of the spleen
Austin (1957)	5 $\frac{1}{2}$		convoluted, collecting and looped tubules (renal biopsy) and urine sediment			
Hain & LaVeck (1958)	2 $\frac{1}{2}$	Kupffer cells	convoluted and collecting tubules	Kupffer cells		
Hagberg, Sounder, Svennerholm & Voss (1959)	4	liver cells, periportal phagocytes	convoluted and collecting tubules	Kupffer cells	convoluted tubules, a few casts in looped tubules	PAS positive material in RES-cells of the spleen.
"	3	liver cells, intrahepatic bile duct walls		Kupffer cells, subendothelial deposits in arteries		In both cases metachromasia in macrophages of the gall bladder

The Kupffer cells did not show any metachromatic deposits. Additional findings in the liver are described in Table 3. *Gall bladder:* the wall showed fibrous thickening. The fundus was 4 mm thick. Cholesterosis, visible to the naked eye, was present. The mucous folds were distended with aggregations of macrophage cells, groups of which contained abundant metachromatic and PAS-positive material. In places slight lymphocytic infiltration was noted. From

other organs no sections were available for histological examination.

CASE 3. Lung: massive purulent bronchitis and the typical histological appearances of acute bronchopneumonia were present. *Liver:* there was slight fatty degeneration particularly in centrilobular regions. Similar to Case 1, metachromatic granules were frequently present in liver cells. PAS-positive material occurred in some of the Kupffer cells. *Gall bladder:* the gall bladder was small

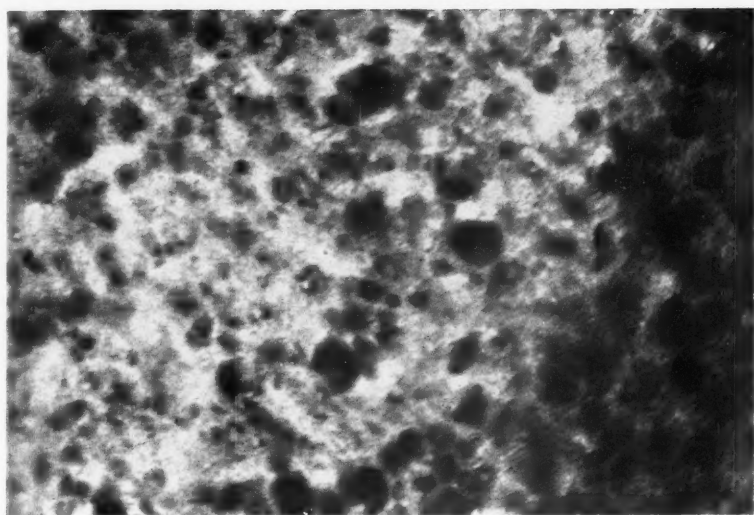


Fig. 6 (Case 3). Frozen section stained with thionin tartaric acid showing red-staining metachromatic material in nerve cells of the dentate nucleus and in surrounding granular bodies $\times 126$ (Kodachrome).

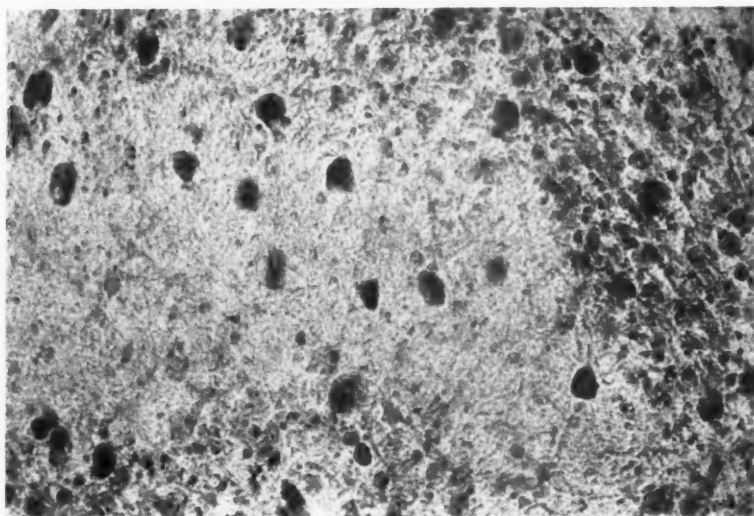


Fig. 7 (Case 3). Frozen section from the same region stained with cresyl violet-acetic acid. Brown metachromatic deposits are present in the nerve cells and in granular bodies. $\times 126$ (Kodachrome).

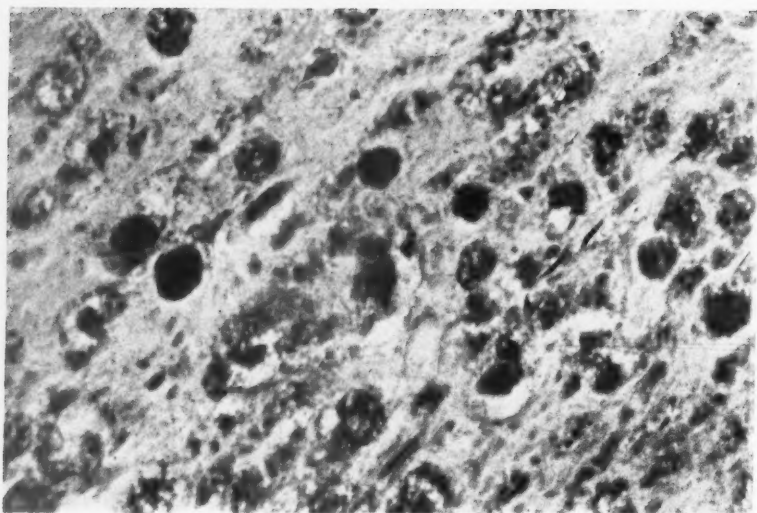


Fig. 8 (Case 3). Granular bodies in the internal capsule giving a positive reaction by the PAS technique. Paraffin section counterstained with Orange G. $\times 126$ (Kodachrome).

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and its wall thickened and firm. It was partly filled with a yellowish friable mass. The histological and histochemical changes were similar to those in Case 1 but less pronounced. *Spleen:* the spleen was somewhat shrunken, the Malpighian corpuscles were small and the pulp was fairly cellular with many mononuclear cells and rather few erythrocytes. There was marked proliferation of the reticuloendothelial cells of the germinal centres. Many of these cells showed PAS-positive material in their cytoplasm. This material did not stain metachromatically. *Kidney:* abundant metachromatic granules were present in the epithelium of convoluted and collecting tubules. PAS-positive material was seen in convoluted tubules (Fig. 9) and in occasional casts. There was no evidence of nephritis.

Sections of pancreas, heart muscle and suprarenal gland revealed no significant histological abnormalities.

Histochemical reactions of the granular bodies

As already described, granular deposits of varying size were present throughout the white matter of both cases, not only in the cerebral hemispheres, cerebellum and brain-stem but also in the spinal cord and its roots. The granular bodies were more abundant in Case 3 than in Case 1. The histochemical reactions of these bodies were identical in both cases, Table 2. Frozen sections were used except for the Feulgen technique. The PAS method was applied on both frozen and paraffin sections. In sections stained with Scharlach R no neutral fat was detected. The positive staining revealed by the Sudan black B method might have been due to the occurrence of phospholipids. The technique of Eigin revealed no free cholesterol after treatment of the sections with digitonin and fat solvents. Sections which did not

undergo this procedure showed blue-green staining of the granular bodies indicating the presence of cholesterol esters. Orcinol-sulphuric acid stained the granules blue-red and Alcian blue stained them brilliant blue. With thionin-tartaric acid deep red metachromasia (Fig. 6) and with cresyl-violet-acetic acid (Fig. 7) equally distinct brown metachromasia was revealed. The reactions given by these four methods indicate the presence of acid carbohydrate compounds in these granular bodies (Table 2). In frozen sections the PAS method for carbohydrates stained the granular material a brilliant purple red. After treatment with chloroform-methanol the granular bodies stained definitely more weakly. This was also the case in paraffin sections (Fig. 8) where a considerable loss of PAS-positive material from the granular bodies had taken place. It may be concluded then that the granular bodies contain both glycolipids and mucopolysaccharides. The Feulgen technique which is specific for deoxyribonucleic acid revealed no nuclear material in the granular bodies.

Autopsy comments

The histopathological findings in our Cases 1 and 3 were essentially similar to those reported by Greenfield (17), Brandberg & Sjövall (10), Brain & Greenfield (9), Leslie (26), Bertrand *et al.* (5), Peiffer & v. Hirsch (21) and Hain & LaVeck (20). In most respects they also resembled those reported by Scholz (21), Bielschowsky & Henneberg (6) and van Bogaert & Scholz (7).

Similar to the case reported by Bertrand *et al.* (5) and diverging from the findings of Brain & Greenfield (9) the optic radia-

tions in our cases were severely affected. Also in our cases a complete disappearance of the oligodendroglia from the white matter of the brain, brain-stem and cerebellum was observed. In the spinal cord a partial loss of these cells from the white matter was found. The number of oligodendroglial nuclei in the cortex and basal ganglia appeared to be normal although some of the perineuronal satellites contained metachromatic and PAS-positive material in their cytoplasm. In general there was more granular deposits in the nerve cells of the cortex, basal ganglia and brain-stem in our cases than in those previously reported. The fact that metachromatic deposits occurred also in the liver cells might be of some importance with regard to the pathogenesis. Chronic cholecystopathy in metachromatic leucoencephalopathy has previously been reported by Norman (28) and Brain & Greenfield (9), and was also obvious in our two cases. At present no conclusions can be drawn as to whether these changes are of primary or secondary importance in this disease.

According to Feigin (15) the staining properties of the granules are not identical in any two cases. In our cases no difference in the histochemical reactions of the granular bodies were seen. In most instances there was nothing to suggest that this material was intracellular. However, the fact that the collections of granules were frequently sharply circumscribed and localized particularly round vessels indicate that it may have been ingested by macrophages.

Clinically muscular hypotonia dominated the initial stage in our cases. The destruction of axons and neuroglial sclerosis were most marked in the cerebellum,

signifying probably early damage in this part of the brain, and possibly indicating a relationship to the initial hypotonia. The increased protein content of the cerebrospinal fluid and the polyradiculitis-like symptoms often observed and by us in Case 3, can be explained by the affection of the nerve roots, which we observed at autopsy.

C. Chemical investigation

Experimental

The left hemisphere was used for the chemical analyses. Material was taken from the superior frontal, pre-central, paracentral, parietal, occipital and temporal gyri. From these parts the grey and white matter were dissected as previously described (34). The grey matter was directly homogenized in an all glass syringe apparatus while the white matter was first cut into sections 20 μ thick on a freezing microtome. Afterwards the material was lyophilized.

The lyophilized material was assayed for nitrogen using the Kjeldahl method, for total hexosamine (33) and total sialic acid (35, 36).

The lipid extractions and the purification of the lipid solutions were performed by the procedure previously described (32). For the analyses of lipid-hexosamine and lipid-sialic acid separate extractions were made (34).

In the lipid extracts total lipids were estimated by a gravimetric method (11). "cholesterol" was assayed according to Zak *et al.* (38), total-phosphorus with a modified procedure of Lowry *et al.* (27), alkali-labile and alkali-stable phosphorus according to Robins *et al.* (31) and cerebroside according to Svennerholm (32).

Cerebrosides and cerebroside-sulphuric acid were separated on mixed bed ion exchange resins columns (37). Ascending paper chromatography was done on Schleicher & Schüll paper 2045 b with tetrahydrofuran-diisobutylketone-water (40:6:5, v/v) and diisobutylketone-acetic acid-water (40:30:5,

TABLE 4. *Composition of grey matter from left occipital lobe. (All figures are calculated as per cent of dry weight.)*

	Case 1	Case 3	Normal
Nitrogen	9.9	9.9	9.8
Hexosamine	0.72	0.73	0.65
N-acetylsialic acid	0.73	0.56	0.48
Total lipids	33.3	28.9	37.3
(except gangliosides)			
Phospholipids	21.1	18.0	25.6
KOH-stable phospholipids	5.7	5.8	5.8
Cholesterol	7.8	6.2	8.3
Cerebrosides	1.8	2.2	1.8
Gangliosides			
Lipid-hexosamine	0.15	0.15	0.14
Lipid-N-acetylsialic	0.45	0.40	0.42

v/v) as solvents. The different lipids were indicated by the dipping technique with the reagents described by Beiss & Armbruster (4). Acid glycolipids were visualized with cresyl-violet in acetic acid (22).

Results and comments

As there was no significant difference between the several parts analysed only

TABLE 5. *Composition of white matter from left occipital lobe. (All figures are calculated as per cent of dry weight.)*

	Case 1	Case 3	Normal
Nitrogen	7.1	7.9	6.5
Hexosamine	0.51	0.69	0.22
N-acetylsialic acid	0.29	0.40	0.18
Total lipids	50.2	42.9	63.4
(except gangliosides)			
Phospholipids	19.2	11.8	29.0
KOH-stable phospholipids	6.0	3.7	7.2
Cholesterol	13.5	9.3	17.7
Cerebrosides (total)	16.2	20.6	16.3
Cerebroside-sulphuric acid	12.4	16.6	2.4
Gangliosides			
Lipid-hexosamine	0.11	0.10	0.05
Lipid-N-acetylsialic acid	0.20	0.22	0.10

the figures for the occipital lobe is recorded in Table 4 and 5. For comparison also the figures for a normal child of two years are given. From Table 4 it is evident that there are only moderate changes in the grey matter. There is a slight decrease in total lipids most pronounced for phospholipids. In both cases only the concentration of alkali-labile phospholipids (glycerophospholipids) is decreased. The changes can wholly be attributed to the formalin fixation as they are of about the same magnitude as those found by Brante (11).

In the white matter the changes are more pronounced than can be explained by the formalin storage, as the brains were placed in formalin only for a short time. The decrease in total lipids was very moderate but there was a strong decrease of phospholipids both the alkali-labile and the alkali-stable ones. The level of cholesterol was decreased especially in Case 3. The concentrations of cerebrosides and gangliosides, however, were within normal limits. At paper partition chromatography the most prominent feature was a large spot of the sulphuric acid esters of cerebrosides. At quantitative estimation these cerebrosides constituted 70–80 % of the total cerebroside fraction. In normal brains sulphuric acid esters of cerebrosides constitute at this age not more than about 10 % of the total cerebrosides but this fraction increases steadily with age up to more than 25 % in senility (37). Thus, the main feature of the lipid disturbance in our cases is a large increase of the sulphate esters of cerebrosides (sulphatides). Jatzkewitz (1958) has recently reported similar findings in a case of the same disease but besides cerebroside-

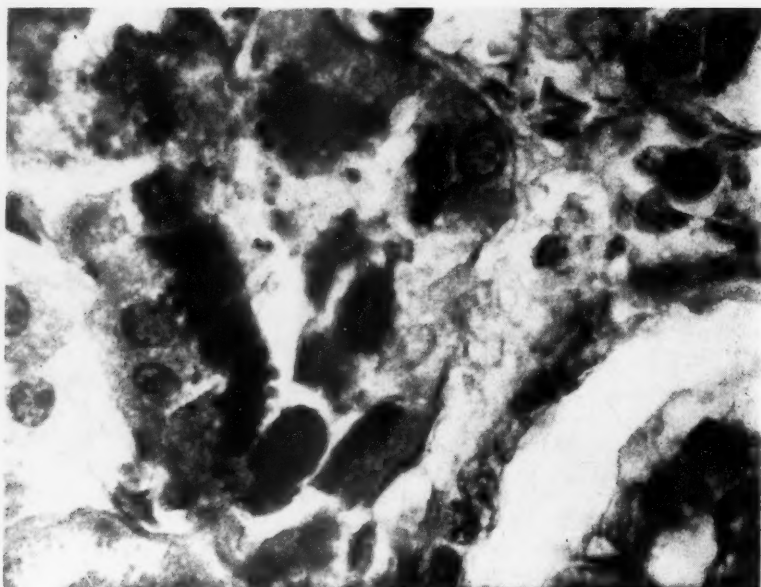


Fig. 9. (Case 3). Kidney. Paraffin section stained by the PAS method showing large amounts of PAS-positive granules in apical parts of tubular cells. Part of a glomerulus is seen in the right lower corner $\times 1100$.

sulphuric acid he also reported the occurrence of a second sulphatide containing a phosphate group. We have not been able to confirm that finding in our cases. Besides cerebroside-sulphuric acid there were also small amounts of other acid glycolipids containing more than one hexose group but they also occur in normal brains in about the same amounts.

Another remarkable feature was the three-fold increase in total hexosamine. As there was only a very slight increase in lipid-hexosamine the increase is mainly attributed to nonlipid-hexosamine which occurs in mucoids and mucopolysaccharides. These findings merit further investigation as there is a concomitant increase of glycolipids and mucopolysac-

charides in neurolipidoses e.g. gargoylism (12), infantile amaurotic idiocy (37).

D. General discussion

Clinical and pathological findings in our cases evidently demonstrate that they belong to the disease entity described by Brain & Greenfield (9) as late infantile metachromatic leucodystrophy. More than one case in the same family has earlier been reported by several authors (1, 5, 7, 10, 28).

The most striking finding of the histological and chemical investigations was the great increase of the sulphuric acid esters of cerebroside (sulphatides). In the white matter there was also a decrease of all

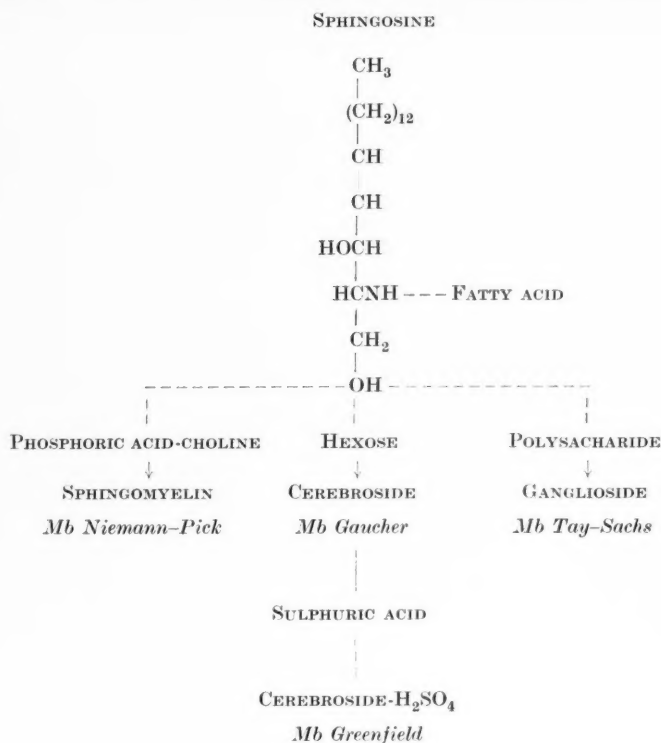


Fig. 10. Diagram showing the close chemical relationship between the neurolipidoses.

the lipids, except glycolipids. A decrease of the lipids is seen in simple demyelination (e.g. Wallerian degeneration) or in diffuse cerebral sclerosis of the Krabbe type but in these conditions there is also marked reduction of the cerebroside. The disturbances in our cases were not only confined to the nervous system but sulphatides were also accumulated in such visceral organs as liver and kidney. Due to the large accumulation of sulphatides in the nervous system and the occurrence of metachromatic substances in the liver cells, macrophages of the gall bladder

and kidney tubules the disease may be classified as a generalized lipidosis (3, 18). It is remarkable that in other diseases belonging to the neurolipidoses there is disturbance in the metabolism of sphingolipids. In Fig. 10 the general structure of the different sphingolipids are outlined with the corresponding diseases occurring as a result of the disturbed metabolism of the actual lipid.

The accumulation of the lipids may be the result of either increased anabolism or decreased katabolism of the lipids. In diseases with known inborn errors of me-

tabolism a lack or decrease of an enzyme is found. If this general pattern is also applicable to the neuropilidoses the various subgroups of these diseases can be explained. From a clinical point of view they are usually classified as an infantile and an adult form but transitions between the two forms exist. In the infantile forms the enzyme deficiency is more complete, while in the adult form it is relatively small. In the present disease most cases are certainly late infantile, but early infantile (14) as well as adult cases (8, 13) have been described.

The sulphatides are normal components of the brain lipids and their concentration increase with age. They are certainly formed from the cerebroside. Radin *et al.* (30) found by giving C^{14} -labelled galactose that the half replacement value for cerebroside was 13 days but that the sulphatides underwent no metabolic breakdown. Judging from their experiments part of the cerebroside is fully metabolized. In the present disease there is an increased content of sulphatides which may be formed in abnormally large amounts from the cerebroside owing to a reduction in the normal breakdown of the cerebroside. The enzymatic mechanism of the normal metabolism of cerebroside is unknown. Possibly the oligodendroglia cells, which are known to have a high metabolic activity, may be of importance (9); and a prominent feature of the present disease is the early disappearance of the interfascicular oligodendroglia (9), irrespective of the degree of demyelination, which we were also able to confirm.

In other pathological conditions of brain, accumulated lipids are ingested by microglia cells and stored as neutral fat.

However, in our two cases we were unable to establish any fat-containing microglia cells and most of the granular material was extracellular indicating an insufficiency of the microglia cells. As these cells are of mesenchymal origin corresponding in function to the reticuloendothelial cells in other organs it was of importance to determine if the sulphatides were stored in the reticuloendothelial cells of the visceral organs examined. In our cases we were unable to detect metachromatic lipids in Kupffer cells of the liver and in reticuloendothelial cells of the spleen. These lipids were mainly accumulated in the parenchymal cells of the liver and the kidney. As most of the lipids are not ingested by the reticuloendothelial cells they are excreted by the kidney in the urine early in the course of the disease (2, 19). They may be demonstrated in the urine of patients either by microscopy of sediments stained with various aniline dyes (1) or by direct chemical analyses for sulphatides (19).

Summary

Clinical, pathological and neurochemical investigations in three boys, two of them brothers, the third second cousin, were performed. The disease started with disturbances of gait at about 1½ years. Progressive neurological signs occurred culminating in death at 3½, 4 and 5½ years, respectively.

In the white matter the myelin sheaths and axons were destroyed and replaced by large amounts of PAS-positive and metachromatic granular bodies. The same substances occurred also in the cortex and basal ganglia, liver, gall bladder and kid-

ney. No oligodendroglia cells were found in the affected white matter.

Chemically the total lipids, mainly the glycerophospholipids, were reduced in the grey and white matter. The total amount of sphingolipids were within normal limits, but there was a great increase of sulphatides.

Leucodystrophie métachromatique tardive de type génétique chez l'enfant

Des recherches cliniques, pathologiques et neurochimiques furent faites chez trois garçons, dont deux sont des frères et le troisième un cousin issu-germain. La maladie commença avec des troubles de la démarche à l'âge de un an et demi. Puis apparition de signes neurologiques se terminant par le décès des patients aux âges de trois ans et trois mois, quatre ans, et cinq ans et trois mois. Dans la substance blanche les gaines de myéline et les axones étaient détruits et remplacés par une grande quantité de corps granuleux PAS-positifs et métachromatiques. Les mêmes substances se retrouvaient dans le cortex et les ganglions basaux, le foie, la vésicule biliaire et le rein. Aucune cellule oligodendroglienne ne fut trouvée dans la substance blanche atteinte. Chimiquement, tous les lipides, principalement les glycérophospholipides étaient réduits dans les substances grise et blanche. La quantité totale de sphingolipides était normale, mais il y avait une grande augmentation de sulphatides. Les découvertes histochimiques et chimiques étayaient la thèse affirmant que cette affection devrait être groupée parmi les sphingolipidoses, et que comme celles-ci elle est due à une erreur innée du métabolisme. Cette affection peut être classifiée comme une lipidose sulphatide.

Eine späte infantile metachromatische Leukodystrophie von genetischem Typ

Es wurden in klinische, pathologische und neurochemische Untersuchungen an drei Jungen, zwei davon Brüder, der dritte Vetter zweiten Grades, durchgeführt. Die Krankheit begann mit Gehstörungen im Alter von ungefähr 1½ Jahren. Es zeigten sich dann fortschreitende neurologische Symptome, die schließlich zum Tode mit 3½, 4 bzw. 5½ Jahren führten. In der weißen Substanz waren die Myelinscheiden und Axone zerstört und durch große Mengen von PAS-positiven und metachromatischen körnigen

The histochemical and chemical findings support the thesis that the disease ought to be grouped among the sphingolipidoses and like these is due to an inborn error of metabolism. It may be classified as a sulphatide lipidosis.

Körpern ersetzt, die auch in den kortikalen und basalen Ganglien, in der Leber, der Gallenblase und in den Nieren zu finden waren. In der betroffenen weißen Substanz fanden sich keine Oligodendroglia. Chemisch gesehen waren die Gesamtlipide, hauptsächlich die Glycerophospholipide, in der grauen und weißen Substanz vermindert. Die Gesamtmenge der Sphingolipide hielt sich in normalen Grenzen; es bestand jedoch eine beträchtliche Vermehrung der Sulfatide. Die histochemischen und chemischen Befunde stützten die These, daß die Krankheit unter den Sphingolipidosen eingruppiert werden muß und, wie diese, auf einem angeborenen Stoffwechselsehler beruht. Sie kann als eine Sulfatidlipidose klassifiziert werden.

Leucodistrofia metacromática infantil tardía de tipo genético

Se han realizado investigaciones clínicas, patológicas y neuroquímicas en tres muchachos, dos de ellos hermanos, el tercero primo segundo. La enfermedad se inició con trastornos de la marcha a la edad de aprox. 1½ años. Se presentaron signos neurológicos progresivos que culminaron con la muerte a la edad de 3½, 4 y 5½ años, respectivamente. En la sustancia blanca estaban destruidas las vainas de mielina y los axones, reemplazados por gran cantidad de cuerpos granulares PAS positivos y metacromáticos. Las mismas sustancias se hallaron también en los ganglios corticales y basales, en el hígado, la vesícula biliar y en los riñones. En la sustancia blanca afectada no se encontraron oligodendroglia. Químicamente, se hallaban reducidos — en las sustancias gris y blanca — los lípidos totales, principalmente los glicérolfosfolípidos. La cantidad total de esfingolípidos se mantenía dentro de los límites normales, pero existía un gran aumento de sulfátidos. Los hallazgos histoquímicos y químicos permiten sostener la tesis de que la enfermedad debe agruparse entre las esfingolipidoses y que, como éstas, se debe a un defecto innato del metabolismo, pudiendo clasificarse como una lipidosis sulfatada.

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Some Constituents of Human Amniotic Fluid in Early Pregnancy¹

by B. WESTIN, J. LIND and A.-C. TEGER-NILSSON

During the past years a considerable amount of information has accumulated about the physical properties and the chemical composition of the amniotic fluid in man and in domestic animals. As regards the domestic animals information has been gained of the composition of the amniotic fluid in different stages of fetal development (5, 10 and others). However, the results are not directly applicable to man, because of differences in placental and fetal development.

In man the interest has mainly been attended to the composition of the amniotic fluid at term (1, 3, 12, 13, 14, 16 and others). In early pregnancy only a few investigations have been made on the composition of the human amniotic fluid (4, 11, 12). The series are generally small and the concentration of potassium has been determined only in a few cases. The protein pattern of the amniotic fluid in early pregnancy appears not to have been studied.

We have therefore collected some data

on sodium, potassium, calcium as well as total and fractional protein concentrations in the human amniotic fluid corresponding to a fetal weight range from 51–750 g.

Materials and Methods

The amniotic fluids were obtained from legally induced abdominal abortions on apparently physically healthy individuals. The fetal membranes were punctured with a needle and the amniotic fluid aspirated with a syringe. Contamination with blood was avoided.

Sodium and potassium were determined with the EEL flame photometer. The standard deviation was 4 per cent for potassium and 3 per cent for sodium.

Calcium was measured according to Kramer & Tisdall (7), and the standard deviation was 1 per cent.

Total amniotic fluid proteins were determined after precipitation in 0.25 M trichloroacetic acid. The precipitate was digested with concentrated H_2SO_4 and H_2O_2 at 270°C for about 15 hours. The ammonia liberated after alkalization was determined after diffusion according to Conway. The standard deviation was 1.8 per cent.

After evaporation to one third of the original volume, the amniotic fluid was subjected to paper electrophoresis in a Kôiv-apparatus with a veronal buffer solution pH 8.6 and

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TABLE 1.

Fetal weight in g	K (mEq/L)			Na (mEq/L)			Ca (mEq/L)		
	Mean	Range	n	Mean	Range	n	Mean	Range	n
51-150	4.1	3.3-4.8	3	142	130-157	3	3.9	3.7-4.1	3
151-250	3.8	2.1-4.5	6	134	108-160	6	3.4	3.2-4.1	6
251-350	4.3	4.0-4.5	2	139	137-140	2	3.6	3.3-3.8	2
351-450	—	—	—	—	—	—	—	—	—
451-550	3.8	3.5-4.0	2	132	131-133	2	3.6	3.5-3.6	2
551-650	5.5	5.2-5.7	2	123	111-134	2	4.8	4.0-5.5	2
651-750	3.8	—	1	134	—	1	3.4	—	1

ionic strength 0.1 (8). The strips were stained in Amido-black and the different fractions were cut out and eluted and were measured in a Beckman B spectrophotometer at 625 m μ . Normal values for plasma of adults and previable human fetuses are indicated in the paper by Westin, Kaiser, Lind, Nyberg & Teger-Nilsson (15).

Results

In Table 1 the concentrations of potassium, sodium and calcium in human amniotic fluid from sixteen cases are related to fetal weights. The mean value for potassium is 4.2 mEq/L with no trend in the potassium concentration when related to fetal weights. The average concentration of sodium is 134 mEq/L. In the weight range 51-350 g the mean value for sodium

is 138 and in the weight range 451-750 g it is 130 mEq/L. but the difference is not statistically significant. The mean concentration of calcium is 3.8 mEq/L and the calcium concentration is independent of the size of the fetus.

In Table 2 are indicated the total protein concentration and the concentrations of albumin and globulin in the amniotic fluid. The total protein concentration averaged at 0.78 g/100 ml.

The mean value for the albumin fraction is 0.58 g/100 ml, and for the globulin fraction it is 0.20 g/100 ml. The albumin/globulin ratio is on an average 2.9. In nine cases (weight range 51-250 g) the mean globulin concentration is 0.10 g/100 ml and in seven cases (weight range

TABLE 2.

Fetal weight in g	Total protein (g/100 ml)			Albumin fraction (g/100 ml)			Globulin fraction (g/100 ml)		
	Mean	Range	n	Mean	Range	n	Mean	Range	n
51-150	0.57	0.36-0.78	3	0.48	0.29-0.65	3	0.09	0.07-0.13	3
151-250	0.50	0.46-0.60	6	0.40	0.34-0.50	6	0.10	0.05-0.14	6
251-350	1.26	0.33-2.76	3	0.82	0.21-1.92	3	0.44	0.12-0.84	3
351-450	—	—	—	—	—	—	—	—	—
451-550	0.74	0.57-0.91	2	0.59	0.50-0.68	2	0.15	0.07-0.23	2
551-650	1.09	—	1	0.79	—	1	0.30	—	1
651-750	0.52	—	1	0.41	—	1	0.11	—	1

TABLE 3.

Fetal weight in g	Globulin fraction (relative %)				
	$\alpha_1 + \alpha_2$	α_1	α_2	β	γ
110	4.6	—	—	5.1	6.9
150	6.7	6.7	—	6.5	5.8
200	10.8	6.0	4.8	7.4	10.8
235	—	—	—	9.4	—
246	9.4	—	—	8.5	9.4
250	8.2	—	—	8.2	—
290	12.4	5.2	7.2	12.0	10.9
495	4.9	—	—	8.4	12.1
495	6.9	—	—	4.9	—
635	4.8	—	—	11.3	11.3
670	14.3	9.9	4.4	2.2	4.4

251–750 g) the corresponding value is 0.25 g/100 ml. The difference is, however, not statistically significant.

In Table 3 is indicated the electrophoretic pattern of the globulin fraction in eleven cases. The α -fraction could be distinguished but the components α_1 and α_2 were only occasionally separated. The mean value of the total α -fraction is 8.3 relative per cent. The β -fraction could be clearly distinguished and the average value is 7.6 relative per cent. When the concentrations of the α - and β -components were compared between the high and low weight groups, no significant differences were found. The values obtained by elution from the γ -region does not necessarily mean presence of γ -globulin. It may as well be due to tailing from other proteins as no clear-cut fraction was visible.

Discussion

The present data for the potassium concentration in amniotic fluid of early pregnancy are in agreement with the results of

McKay, Roby, Hertig & Richardson (11) and Davies (4) and of the same order as the term values. In early pregnancy the sodium concentration of the amniotic fluid appears to be slightly higher than that at term (4, 12). The explanation has been brought forward that this is due to dilution of the amniotic fluid with hypotonic urine.

The concentrations of sodium and potassium respectively are approximately the same in the amniotic fluid and the maternal plasma. According to Westin *et al.* (15), however, the concentrations in fetal plasma are markedly higher; the mean potassium concentration has been given as 9 mEq/L and the mean sodium concentration as 155 mEq/L.

The fetus thus can maintain a higher concentration of these ions not only than the maternal plasma but also than the amniotic fluid. Similar and much larger differences in potassium concentrations have been found between amniotic fluid and allantoic fluid in the rabbit (5, 6) and in the pig (10).

The calcium concentration in the amniotic fluid remains constant but is slightly lower than that in fetal and maternal plasma. This parallels the findings that the calcium concentration in fetal plasma remains constant (15) and is equal to the calcium concentration in normal adults in spite of the rapidly increasing total body calcium of the fetus.

The protein concentration in the amniotic fluid of small fetuses is considerably lower than that in maternal (9) and fetal plasma (15) and seems to remain constant in the fetal weight range now investigated. However, the total protein concentration is approximately twice the value

reported by Candiani (3) for amniotic fluid at term (viz. 0.35 g/100 ml).

The albumin/globulin ratio in the present material is 2.9 and in agreement with the value given by Candiani (3) for amniotic fluid at term. This ratio thus seems to remain constant during the period of gestation and to be independent of changes in the maternal and fetal plasma protein concentrations.

In the globulin fraction we have only been able to demonstrate the α - and β -globulins. Neither γ -globulin, nor prealbumin or fraction-X (2, 15) of fetal plasma has been found in the amniotic fluid by the present technique. This is in accordance with the protein pattern of the amniotic fluid at term (3).

Summary

The human amniotic fluid of previable human fetuses has been analyzed in sixteen cases in the fetal weight range 51–750 g. The concentration of potassium is approximately constant and the mean value is 4.2 mEq/L. The average concentration of sodium is 134 mEq/L and when compared with term values there is a trend towards decreasing sodium concentration with increasing fetal development. The concentration of calcium is approximately constant and the average value is 3.8 mEq/L.

The total protein content of the amniotic fluid is on an average 0.78 g/100 ml. The mean value is 0.57 g/100 ml for albumin and 0.20 g/100 ml for globulin. In eleven cases (fetal weight 110–670 g) alpha- and betaglobulin could be distinguished. The albumin/globulin ratio is on an average 2.9.

Quelques constituants du liquide amniotique humain au début de la grossesse

Le liquide amniotique humain a été analysé chez 16 fœtus humains préviabiles dont le poids variait entre 51 et 750 gr. Les concentrations de potassium étaient approximativement les mêmes et la moindre était de l'ordre de 4,2 mEq/lit. La concentration moyenne de sodium était de 134 mEq/lit et la concentration du sodium avait tendance à décroître avec l'accroissement du développement fœtal. La concentration de calcium était approximativement constante et la moyenne était de l'ordre de 3,8 mEq/lit. Le liquide amniotique renfermait une moyenne de 0,78 g%. La valeur la moindre était de 0,57 g% pour l'albumine et de 0,20 g% pour la globuline. Pour onze cas (d'un poids fœtal variant entre 110 et 670 g) il été possible de distinguer les globulines alpha et beta. Le rapport albumine/globuline était de 2,9.

Einige Bestandteile der menschlichen Fruchtblüssigkeit während der frühen Schwangerschaft

Die Fruchtblüssigkeit bei präviablen menschlichen Fötussen ist in 16 Fällen analysiert wor-

den, wobei das Fötusgewicht zwischen 51 und 750 Gramm lag. Die Kaliumkonzentration war ungefähr konstant; der Mittelwert betrug 4,2 Milliäquivalente/Liter. Die mittlere Natriumkonzentration betrug 134 Milliäquivalente/Liter, und es schien eine Tendenz zu abnehmender Natriumkonzentration bei fortschreitender Entwicklung des Fötus zu bestehen. Die Kalziumkonzentration war annähernd konstant; der Mittelwert betrug 3,8 Milliäquivalente/Liter. Der Gesamtproteingehalt der Fruchtblüssigkeit betrug im Mittel 0,78 g%. Der Mittelwert war 0,57 g% für Albumin und 0,20 g% für Globulin. In elf Fällen (Fötusgewicht 110–670 Gramm) konnten Alpha- und Betaglobulin unterschieden werden. Das Albumin/Globulin-Verhältnis betrug 2,9.

Algunos componentes del líquido amniótico humano en la gestación incipiente

Se ha analizado el líquido amniótico de 16 fetos humanos previables, cuyos pesos oscilaban entre 51 y 750 gramos. La concentración de potasio era aproximadamente constante y el valor medio de 4,2 miliequivalentes/litro. La

concentración media de sodio era de 134 miliequivalentes/litro, pareciendo que había cierta tendencia a una concentración decreciente de sodio pareja al aumento del desarrollo del feto. La concentración de calcio era aproximadamente constante y el valor medio de 3,8 miliequivalentes/litro. El contenido total en proteína, del

líquido amniótico, era al promedio de 0,78 g%. El valor medio era de 0,57 g% para albúmina y de 0,20 g% para globulina. En once casos (pesos fetales entre 110 y 670 gramos) era posible distinguir las globulinas alfa y beta. La proporción de albúmina/globulina era de 2,9.

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Discrete Examination of Tubular Reabsorption of Water in Children's Kidneys

by LIBUŠE HRADCOVÁ and OTA SCHÜCK

Cases necessitating a separate examination of each kidney are often encountered in our clinical practice. The normal values of renal function obtained through the analysis of mixed urine from the bladder in the course of routine medical examination does not necessarily indicate normal function of both kidneys. One of them may be severely disturbed but the other one may compensate for the former's inadequate function. If a unilateral or asymmetric disturbance of the kidneys is suspected, it is necessary both for the sake of the diagnosis and of the therapy to determine the function of each kidney separately. Findings of intravenous urography are commonly used for this purpose. But this examination method allows for only a rough estimate of renal function. The application of modern clearance methods is in the case of separate examination rendered difficult by the quantitative collection of urine from each kidney separately and by the difficulty of maintaining a constant concentration of the substance under study in the plasma. They are therefore not suitable for routine clinical practice.

In our previous papers concerning the problems of separate examination of the kidneys of adults we have shown that it

is possible to ascertain a number of renal functions even without precise knowledge of urine volume (Schück & Hradec (4)).

Separate examination of the tubular reabsorption of water has appeared to be most suitable for practical purposes (Schück & Hradec (5)). This function can be determined from the value of the concentration index of the non-threshold substance, i.e., from the ratio between concentration in urine and in plasma. From these values it is possible to calculate tubular reabsorption of water in glomerular filtration percentages. The suitability of this method for routine examination of adults has lately been confirmed by Prát (3).

It is the purpose of this paper to determine whether the method of separate examination of tubular reabsorption of water is suitable also in pediatrics.

Methods

The determination of separate tubular reabsorption of water (TRW) was conducted in the course of normal urological examination; which did not make it necessary to prepare the child in any special way. In order to exclude a reduction of TRW due to water diuresis the examined patient drank 100 ml of tea on an empty stomach in the morning, after which further intake of fluid

was strictly forbidden. The urological examination was carried out four hours after the patient had taken the tea. The children in question were, as may be seen, not prepared for the usual examination of the maximum concentration power of the kidneys. A cystoscope was introduced to collect urine from the urinary bladder to determine TRW from both kidneys. This was followed by the introduction of a soft ureteral catheter No. 3-4 Charr. into the upper half of the ureter or even up to one pelvis or simultaneously up to both of them. The time of collection of urine dropping from the ureteral catheter into a test tube differed according to the intensity of the diuresis. In some instances more specimens of urine were collected. As 0.1 ml of urine is necessary for its analysis it is sufficient to collect a few drops of urine only. If one catheter only was introduced into one of the pelves, bladder-urine was in none of the cases used for examination after the introduction of the catheter because urine from both kidneys was mixed in the bladder in a different ratio. This was so because obturation catheters were never used. After the conclusion of the urological examination, blood was drawn from the vena cubitalis. One tenth ml of urine was sucked into a pipette and diluted with 10 ml of distilled water (the urine was diluted 101 times). In the urine and plasma specimens the concentration of endogenous creatinine (Bonsnes & Taussky (1)), which can be considered for practical purposes as a non-threshold substance, was determined. The concentration of endogenous creatinine in urine (U) and in plasma (P) thus found made it possible to calculate:

1. The concentration index U/P . The value of the concentration index is, in a non-threshold substance, directly dependent on the intensity of the reabsorption of water in the tubules. Under normal conditions the value of this index in children ranges from 50 to 300.

2. Tubular reabsorption of water in glomerular filtration percentages (TRW). Under normal conditions the value of TRW ranges between 98.0% and 99.7%.

If the number of ml of water reabsorbed in the tubules in one minute is marked C_{H_2O} , the glomerular filtration GF and diuresis V , both of which are calculated in terms of one minute, the following equations apply:

$$T_{H_2O} = GF - V, \quad GF = \frac{VU}{P}.$$

The ratio between T_{H_2O} and GF can be calculated without precise knowledge of the urine volume.

$$TRW = \frac{T_{H_2O}}{GF} \cdot 100 = \frac{GF - V}{GF} \cdot 100 = \left(1 - \frac{P}{U}\right) \cdot 100.$$

The advantage of this formula lies in the fact that it does not require the quantitative collection of urine.

We have examined in this way a total of 40 children aged $1\frac{1}{2}$ to 15 years. Some of them have been examined several times. All of the children were hospital patients and bore the urological examination very well. Neither a rise in temperature nor any infection of the urinary tract has ever been found after the examination. In the vast majority of children the following renal functions were examined several days before the urological examination: 1. clearance of endogenous creatinine (C_{CR}) and TRW; the values of C_{CR} were recalculated per 1.73 square metres body surface area; 2. maximum concentration power of the kidneys (MCP) during a period of 36 hours when no fluids were given to the patient; 3. maximum dilution power after the intake of 500 to 1000 ml of water (according to the age and weight of the child). Addis sediment was also examined in most children. Intravenous urography was carried out in each child and in some cases retrograde pyelography and possibly also pneumoretroperitoneum or abdominal aortography, were done.

Results

The results of the examinations may be found in Tables 1 to 4 which show the

values of the concentration indices of endogenous creatinine (invariably the highest values of U/P from a whole series of specimens). At the same time the most important data relating to the examined children are given.

It is necessary to emphasize that the separate examination of the tubular reabsorption of water, the examination of glomerular filtration as well as of the maximum concentration power and the maximum dilution power were conducted consecutively on different days, while the patients were in hospital.

Table 1 shows 18 children with X-ray proven uni- or bilateral hydronephrosis. It follows from the results that the value of the concentration index was in 15 cases higher than 50. But in the first case there was asymmetry in the simultaneous collection of urine from both kidneys and on the side of the hydronephrosis U_S/P is lower. In the case of pathological values of U_M/P there was a simultaneous grave pyelonephritis in the 9th and 14th Case and the low values of U_M/P point to a significant involvement of both kidneys. In the 11th Case there was an enormous hydronephrosis. The difference in the U_S/P values in the 10th Case when examination was repeated within half a year is explained by an improvement in the function of the hydronephrotic kidney after a plastic operation on the horseshoe-shaped kidney complicated by hydronephrosis on the left side. A comparison between the U_M/P values obtained immediately before examination with the values of U/P obtained during spontaneous urination not during urological examination reveals that all the U_M/P values are lower (with the exception of the 3rd and 16th Case). The endogenous creatinine clearance values are within the limits of normal with the exception of Cases 9 and 11. The maximum concentration power was reduced below the normal value (1028) in eight cases, i.e. in nearly half the cases. But the dilution

power of the kidneys was never disturbed; with the exception of Case 8 where the specific gravity of urine did not drop under 1.003 (the normal value is 1.001–1.003). In most cases there was an increase of leucocytes in the urine sediment pointing to additional infection. Granulated cylinders were never found. The intensity of the proteinuria ranged from a negative finding up to $++$.

Table 2 shows seven cases in which infection in the urinary tract was clinically diagnosed. Pyelonephritis with an asymmetric involvement of the kidneys was obviously present in Cases 1, 3, 4 and 6. On the other hand in Case 2 asymmetric involvement of the kidneys was not marked in agreement with the minimum clinical findings. In Cases 5 and 7 only the affected kidney was examined. In Cases 1, 4 and 6 the results of concentration indices differed even on the same side because of a time lag. In Case 1 the tubular function was considerably improved after nephrolithotomy when infection had been controlled and the urine sterilised. In Cases 4 and 6 the disease was of a progressive character and the values U_S/P (Case 4) and U_D/P (Case 6) were clearly lower when examined for the second time than when the examination was carried out originally. The C_{CR} values were normal in all cases in this group. The maximum concentration power was reduced four times and became normal in some patients in the course of treatment. The maximum dilution power was in all cases normal. The urine sediment of all patients contained numerous and even countless leucocytes while proteinuria was only very slight.

Table 3 consists of four cases of congenital anomalies: two cases of ren arcuatus, one case of unilateral ren duplex et ureter duplex and one case of hypoplasia of the kidney. None of the cases were complicated by infection; proteinuria was very slight. Findings on the right side in the horseshoe-shaped kidneys, in the upper and lower right kidney in the case of doubling and in the congenital hypoplastic kidney point towards a normal state of TRW.

Table 4 comprises ten cases where internal

TABLE 1. *Separate examination of tubular reabsorption of water in hydronephrosis.*

P denotes concentration of endogenous creatinine in plasma, U in bladder urine from both kidneys obtained by spontaneous urination, U_M in bladder urine from both kidneys collected before introducing the catheter into the ureter, U_D in urine from the right kidney, U_S in urine from the left kidney. $T_{MH_2O}/(GF) \cdot 100$ denotes tubular reabsorption of water in glomerular filtration percentage from both kidneys simultaneously before introducing the catheter whereas $T_{DH_2O}/(GF)_D \cdot 100$ and $T_{SH_2O}/(GF) \cdot 100$ denote tubular reabsorption in the right and in the left kidney respectively. C_{CR} represents the average value of clearance of endogenous creatinine recalculated to the 1.73 square metres body surface area, MCP denotes maximum concentration power. These findings demonstrate that hydronephrosis alone unless too extensive and unless complicated by advanced pyelonephritis need not lead to a lowering of tubular reabsorption of water.

Number	Sex	Age in years	Clinical diagnosis	$\frac{U_M}{P}$	$\frac{U_D}{P}$	$\frac{U_S}{P}$	$\frac{T_{MH_2O}}{GF} \cdot 100$	$\frac{T_{DH_2O}}{GF_D} \cdot 100$	$\frac{T_{SH_2O}}{GF_S} \cdot 100$	C_{CR} ml/min	$\frac{U}{P}$	MCP
1.	F	11 11½ 12	Left hydronephrosis, Chronic left pyelonephritis	60		56	98.4		98.3	100.6	200	1028
				57	208	93	98.3	99.5	98.9	91.8	143	1020
				74		93	98.6		98.9	135.4	143	1020
2.	F	8	Bilateral hydronephrosis, Chronic bilateral pyelonephritis									
3.	F	9 10	Right hydronephrosis, Chronic right pyelonephritis	136 103	53 50	89	99.3 99.0	98.6 98.0	98.9	99.0	125	1028
4.	F	8	Bilateral hydronephrosis, Chronic bilateral pyelonephritis									
5.	M	8 8½	Right hydronephrosis, Chronic right pyelonephritis	68 62	74 69		98.6 98.4	98.6 98.6		126.2	166	1016
			Right nephrolithiasis	80	51		98.8	98.1		92.6 108.3 97.1	333 89	1031 1025
6.	F	8	Left hydronephrosis	104		85	99.0		98.8		166	1025
7.	M	7	Left hydronephrosis	175		133	99.4					
8.	F	7	Left hydronephrosis	129		82	99.2			168.2	200	1034
9.	M	5	Right hydronephrosis, Right pyelonephrosis							188.5	250	1030
10.	M	14½ 15	Left hydronephrosis, Ren arcuatus State after symphysiotomy and resection of the left pelvis	13 71	12 32		92.1 98.6	91.6	97.0	60.6 98.4	62 143	1025
11.	M	5	Huge left hydronephrosis, Left hydronephrosis	111		130	99.1		99.2	84.9	143	1025
14.	F	1½	Left hydronephrosis, Chronic bilateral pyelonephritis	30 33 28		10 21 20	100.7 100.9 100.4	95.3	97.5 95.0	69.7	18	1020

TABLE 2. *Separate examination of tubular reabsorption of water in patients, suffering from urinary tract infection.*

In the cases of pyelonephritis asymmetric effects on the tubular reabsorption of water may be found.

Number	Sex	Age in years	Clinical diagnosis	$\frac{U_M}{P}$	$\frac{U_D}{P}$	$\frac{U_S}{P}$	$\frac{T_{MH_2O} \cdot 100}{GF}$	$\frac{T_{DH_2O} \cdot 100}{GF_D}$	$\frac{T_{SH_2O} \cdot 100}{GF_S}$	C_{CR} ml/min	$\frac{U}{P}$	MCP
1.	M	11	Right nephrolithiasis, Chronic right pyelonephritis	81	22	147	98.7	95.5	99.3	141.6	125	1021
		11½	State after nephrolithotomy	150	44		99.3	97.8		113.9	67	1028
2.	M	3	Left nephrolithiasis, Chronic left pyelonephritis	80	60	75	98.7		98.6	102.0	200	1024
		3½		138	69	63	98.4	98.6	98.4	81.4	333	1030
3.	F	10	Bilateral nephrolithiasis, Chronic right pyelonephritis	197	7	144	99.5	85.8	99.3	105.6	166	1031
4.	M	7	Left nephrolithiasis, Chronic left pyelonephritis	63	219	76	98.4	99.5	98.6	120.4	143	1027
		7½		84	24	49	98.8	95.7	97.9	161.1	200	1031
5.	F	3	Right nephrolithiasis, Chronic right pyelonephritis	77	36		98.7	97.2		80.0	166	1030
6.	F	9	Cystosis renum. Chronic bilateral pyelonephritis	46	52	42	97.8	96.0	97.7	126.1	143	1023
		10		27	10		98.0			235.2	143	1018
7.	F	8	Cystitis bullosa. Chronic pyelonephritis	27			96.3		89.5	163.1	143	1028

TABLE 3. Cases of congenital renal anomalies which alone need not cause a disturbance of tubular reabsorption of water.

Number	Sex	Age in years	Clinical diagnosis	$\frac{U_M}{P}$	$\frac{U_D}{P}$	$\frac{U_S}{P}$	$\frac{T_{MHO}}{GF} \cdot 100$	$\frac{T_{DHO}}{GF_D} \cdot 100$	$\frac{T_{SHO}}{GF_S} \cdot 100$	C_{CR} ml/min	$\frac{U}{P}$
1.	M	15	Ren arcuatus	111	211		99.1	99.5			
2.	F	8	Doubled right kidney and right ureter	98*	79**			98.9*			1032
3.	M	12	Ren arcuatus		53			98.7**			
4.	M	8	Congenital hypoplasia of right kidney	80	266		98.8	98.1		145	89 1033
								99.6		118.2	125 1035

* Upper right kidney.

** Lower right kidney.

TABLE 4. Control group.

In Cases 9 and 10 reflex reduction of tubular reabsorption of water is shown.

Number	Sex	Age in years	Clinical diagnosis	$\frac{U_M}{P}$	$\frac{U_D}{P}$	$\frac{U_S}{P}$	$\frac{T_{MHO}}{GF} \cdot 100$	$\frac{T_{DHO}}{GF_D} \cdot 100$	$\frac{T_{SHO}}{GF_S} \cdot 100$	C_{CR} ml/min	$\frac{U}{P}$
1.	F	3	Cured ac. cystitis		89	51	99.5	98.8	98.0	153.4	200 1038
2.	F	3	Orthostatic proteinuria		99	65		98.9	98.5	118.1	125 1031
3.	F	4	Cured ac. cystitis	52		393	98.1		99.8	120.0	333 1036
4.	M	3	Chronic tonsillitis			91			99.0	89.9	250 1032
5.	F	9	Enuresis nocturna	96	193		99.0	99.5		119.2	89 1035
6.	F	5½	Cured ac. cystitis	103		99	99.0		99.0	108.6	250 1034
7.	M	13	Enuresis nocturna	151	213		99.3	99.5		119.7	166 1031
8.	M	13	Chronic tonsillitis	91	208		98.9	99.5		155.0	166 1032
9.	F	10	Hypotonia of the left ureter	132	15	11	99.2	93.5	90.8	158.0	142 1030
10.	F	8	Left ren migrans	33	28			97.0	96.4	109.0	91 1037

and urological findings were normal or only a slight proteinuria was ascertained. The first case points to normal state of TRW in both kidneys. The difference between the right and left kidney was as in Case 2 probably due to the fact that the urine specimens were not collected during the same period. Cases 3-8 also show normal TRW in the examined kidney. Cases 9 and 10 exemplify reflex reduction of TRW. In the ninth Case it is believed to be due to the fact that the U_D/P , U_S/P values in both kidneys are significantly lower than the U_M/P before the introduction of the ureteral catheters and in the tenth Case it is so because the U_D/P , U_S/P levels in both kidneys are considerably lower than U/P of urine obtained in the course of spontaneous urination.

Discussion

In evaluating the findings of separate examination it is always necessary to take account of the possibility of a reflex lowering of TRW connected with instrumental urological examination. It is not yet clear whether the lowering of TRW is caused, under these circumstances, by irritation of the urinary tract or by the accompanying emotions (Miles & de Warden (2)). But emotional influence on TRW is also manifested in that the U_M/P values shortly before the application of the catheters to the ureters are usually lower than the U/P values found a few days before this examination when spontaneous urination occurred. As U/P does not fall, in the case of healthy children, below 50 within 24 hours when there is a normal intake of fluid; it may be assumed that wherever U/P is 50 or higher, TRW is not seriously damaged. But it is impossible to deduce from the TRW value determined during the urological examina-

tion what the maximum concentration power of the examined kidney may be. If we find in the course of separate examination that the concentration index value is 50 or more we can assume that TRW has not been disturbed. In this case separate examination makes it possible to exclude severe tubular disturbances. Where the concentration index is under 50 it is necessary to decide whether the lowering is due to a pathological process in the kidney or whether it is a reflex reaction.

We are guided by the following circumstances when distinguishing between the two possibilities:

1. Reflex reduction of TRW is indicated by lower concentration index values in both kidneys than in the undifferentiated urine from the bladder.

2. The concentration index often varies with time when reflex lowering is the cause. The Figure (Case S.J.) shows an example of sudden reflex changes of TRW where the concentration index falls from normal values to pathological ones and again rises rapidly towards the normal. On the other hand if the kidney is pathologically disturbed, oscillation of the concentration index back towards normal values is impossible (Figure, Case H.J.).

3. Low values of the concentration index on one side only while there are normal values on the other side at the same time point to a pathological origin of the lowering of TRW.

All this shows that it is advantageous for the evaluation of the findings to compare the findings from each kidney with the values before the application of the catheters and that it is correct and advantageous to collect a greater number of specimens from each kidney.

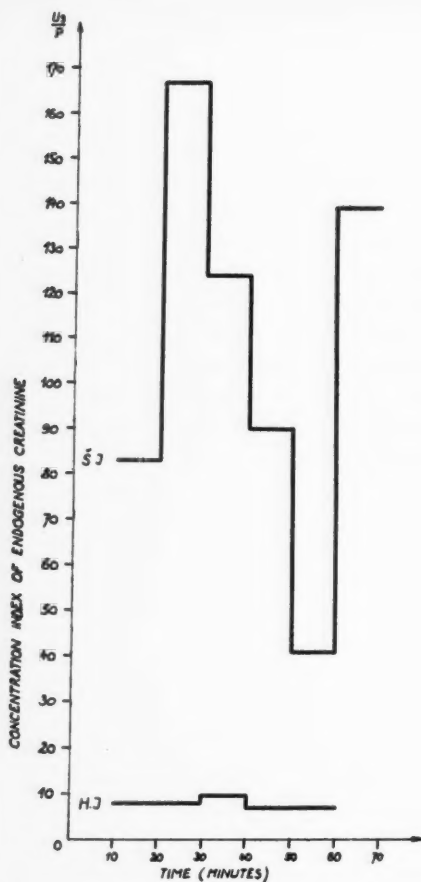


Fig. 1. The figure shows an example of quick reflex changes in concentration index in Case S. J., a boy aged 8 years suffering from subacute glomerulonephritis. The case is not included in the tables.

$C_{CR} = 216.0$ ml/min/1.73 square metres, $U/P = 200$, $T_{H_2O}/GF \cdot 100 = 99.5\%$. MCP 1026.

Case H. J. (Table 2, No. 7) shows permanently pathologically reduced values of the concentration index in the disturbed kidney.

Our findings demonstrate that hydronephrosis alone, unless too extensive and unless complicated by advanced pyelonephritis, need not lead to a pathological lowering of TRW, i.e., a drop below 98%.

In the case of pyelonephritis we have often found an asymmetric effect on TRW in either kidney. Congenital anomalies alone need not cause a disturbance of TRW.

The above-mentioned information reveals the practical value of separate examination of TRW, especially in the case of urological diseases which are very often complicated by infection usually resulting in pyelonephritis. The latter is often an asymmetric disease and affects the tubular function of the nephron first and most severely. The separate examination of TRW is a simple method, clinically useful, and not exacting as far as laboratory work is concerned. This is a special examination conducted by us only in specially indicated cases. However, whenever it is for any reason necessary to insert a catheter into the ureter we always examine the TRW at the same time.

Summary

The tubular reabsorption of water in the kidney was discreetly examined in 40 children aged $1\frac{1}{2}$ to 15 years. Eighteen of these were cases of hydronephrosis, seven patients suffered from an infection of the urinary tract or from pyelonephritis, one from glomerulonephritis, four children had congenital renal anomalies and the remaining ten children had no pathological findings or had only slight proteinuria. Unless complicated by pyelonephritis in the case of patients suffering from hydronephrosis the tubular reabsorption of water was normal, i.e., not below 98%. The group suffering from infection of the urinary tract often revealed either asymmetry in the effect on the kidneys or lowering of the function under study. The

values of tubular reabsorption of water were normal in the case of anomalies and in the control group.

The separate examination of the tubular reabsorption of water is a simple, clinically useful method which aids in the diagnosis of specially indicated cases. In the evalua-

tion of the findings it is necessary to exclude the possibility of a distortion of the findings by a reflex lowering of the tubular reabsorption of water, caused by instrumental examination and the patient's emotional state.

Examen séparé de la réabsorption tubulaire de l'eau dans le rein de l'enfant

La réabsorption tubulaire de l'eau dans le rein fut examinée séparément chez 40 enfants âgés de un an et demi à quinze ans. Dix-huit de ces cas étaient atteints d'hydro-néphrose, sept patients souffraient d'une infection des voies urinaires ou de pyélonéphrite, un de glomérulonephrite, quatre enfants avaient des anomalies rénales congénitales et les dix autres n'avaient aucune affection pathologique ou seulement une légère trace de protéine dans l'urine. La réabsorption tubulaire de l'eau était normale (pas inférieure à 98 %) chez les malades souffrant d'hydro-néphrose, si leur cas ne se compliquait pas de pyélonéphrite. Le groupe atteint d'infection des voies urinaires présentait souvent, soit une asymétrie intéressant les reins ou une diminution de la fonction étudiée. Les taux de réabsorption de l'eau étaient normaux pour les cas d'anomalies et pour le groupe de contrôle.

Einzeluntersuchung der Tubularreabsorption des Wassers in den Nieren der Kinder

Bei 40 Kindern im Alter von 1½ bis 15 Jahren wurde die Tubularreabsorption des Wassers in den Nieren einer Einzeluntersuchung unterzogen. 18 dieser Fälle waren Hydronephrosen, 7 litten an einer Infektion des Harntrakts oder einer Pyelonephritis, 1 hatte Glomerulonephritis, 4 Kinder hatten angeborene Nierenanomalien, und die restlichen 10 wiesen keine patholo-

gischen Befunde auf oder hatten nur eine leichte Proteinurie. Abgesehen von Komplikationen durch Pyelonephritis im Fall der an Hydro-nephrose leidenden Patienten, war die Tubularreabsorption des Wassers normal, d.h. sie lag nicht unter 98 %. Die an einer Harntraktusinfektion leidende Gruppe zeigte oft entweder eine Asymmetrie hinsichtlich der Rückwirkungen auf die Nieren oder ein Nachlassen der untersuchten Funktion. Bei den Fällen von Anomalien und in der Kontrollgruppe waren die Tubularwasserreabsorptionswerte normal.

Estudio particular de la reabsorción tubular del agua en los riñones de los niños

En 40 niños de 1½ a 15 años se sometió a estudio particular la reabsorción tubular del agua en los riñones. 18 de estos casos eran hidronefrosis, 7 padecían una infección del aparato urinario o una pielonefritis, 1 tenía glomeronefritis, 4 niños presentaban anomalías renales congénitas y los restantes 10 niños no ofrecían ningún hallazgo patológico o solamente una ligera proteinuria. Salvo en caso de complicación por pielonefritis en los pacientes afectados de hidronefrosis, la reabsorción del agua era normal, es decir, no inferior al 98 %. El grupo que sufría una infección del aparato urinario revelaba a menudo ya una asimetría en la afección renal, ya una disminución de la función en estudio. Los valores de la reabsorción tubular del agua eran normales en el caso de anomalías y en el grupo de control.

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CASE REPORT

Essential Hypercholesterolaemia in Two Siblings

Effect of Corn Oil on Serum-Lipoids

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Familial essential hypercholesterolaemia with or without xanthomatosis is not uncommon in adults (8, 10), but in children, especially in combination with xanthomatosis, it is a rarity (6, 15).

The hereditary nature of the disease has been established, and the Scandinavian workers Müller (13, 14), Svendsen (19), Kornerup (10), and others, consider that the transmission follows a dominant pattern, while according to, for instance, Wilkinson *et al.* (20) it is transmitted as an incomplete dominant trait.

The disease is characterized by raised serum-cholesterol with onset in childhood. There are no marked sex differences. If serum-cholesterol is maintained at a not too high level (325-400 mg per 100 ml), hypercholesterolaemia may remain the only evidence of the condition throughout the person's life-time (15, 16). If it reaches higher values, there may occur additional symptoms in the form of xanthelasma palpebrum, xanthomas particularly and most typically over tendons and periarticular fasciæ and tissues, and deposition of cholesterol in the vascular system. Essential hypercholesterolaemia occurs in children and adolescents usually as the only

symptom of the disease, while the risk for xanthomatosis becomes greater with increasing age. As a rule, essential hypercholesterolaemia in children is detected during investigations of families of patients with the disease. By a follow-up of Kornerup's (10) large material of familial essential hypercholesterolaemia in Denmark Piper & Orrild (15, 16) found that the youngest patient with xanthomatosis was 19 years old, while there were a further 36 children and youths under 20 years, of whom 25 were less than 10 years old, who had only hypercholesterolaemia.

In the differential diagnosis it is important to consider other diseases that may be associated with raised serum-cholesterol levels, such as hypothyreosis, the nephrotic syndrome, diabetes mellitus, and essential hyperlipaemia. In a number of the relatively few published cases of hypercholesterolaemia with xanthomatosis in children complete serum-lipoid analyses were not done, and, therefore, the diagnosis of familial essential hypercholesterolaemia is often questionable (7, 17), since, for instance, essential hyperlipaemia may have been present.

The prognosis of the disease is uncer-

TABLE 1. *Blood lipids and lipoproteins in the family. Values in mg per 100 ml serum.*

	Choles- terol	Phospho- lipids	Glyceri- des	α -lipoproteins		β -lipoproteins	
				Choles- terol	Phospho- lipids	Choles- terol	Phospho- lipids
Father	230	230	130	50	100	170	120
Mother	550	440	94	40	85	490	340
G. M.	410	300	92	50	85	345	200
L. M.	400	310	80	55	105	330	200

tain. Sudden death from coronary sclerosis is more common in families with hypercholesterolaemia than it is in those who have normal cholesterol levels (1, 2, 7, 15). If xanthomatosis appears in children with essential hypercholesterolaemia this may later lead to early sudden death from heart disease.

Kornerup described a young man who died suddenly at the age of 18 years, probably from coronary occlusion. The patient had developed marked xanthomatous lesions since the age of 3 years. Cook *et al.* (6), in 1949, reported a well-documented case of essential hypercholesterolaemia with xanthomatosis in a 13 year old boy. Besides xanthomas of the elbows, knees and thighs, he had also electrocardiographic evidence of coronary sclerosis. The boy died suddenly a year later. The clinical observations were verified at necropsy. Maker *et al.* (11) reported the necropsy findings in two children in a family with essential hypercholesterolaemia, where the parents were alive and well with hypercholesterolaemia, while 6 of 18 children had died from probable xanthomatous heart disease. These two children who died at the age of 12 and 16 years, respectively, were at necropsy found to have advanced coronary arterial disease (11).

Since the autumn of 1957 we have had the opportunity of studying a 10 year old girl with essential hypercholesterolaemia and xanthomatosis. She belongs to a family of four members of whom only the

father is in good health and has fully normal values for blood-lipoids (see Table 1). The mother and the 9 year old sister both have hypercholesterolaemia, the former with and the latter without xanthomatosis.

By this report we wish to draw attention not only to the uncommon finding of xanthomatous lesions appearing in a girl only 10 years old with familial essential hypercholesterolaemia, but also, and in particular, to the fact that it now seems possible to lower the serum-cholesterol level by increasing the amount of unsaturated fatty acids in the diet and, thus, by this prophylactic dietary treatment, to improve the prognosis.

Case Reports

Case 1. A girl, L. M., born on April 25, 1945. She was very susceptible to infections. She had marked allergic disorders in the form of hay-fever and urticaria, for which she had undergone special allergological investigation. In 1956 she had had acute otitis media and shortly afterwards swelling and tenderness of the joint of the great toe. Because of this she had attended the Out-Patient Department for examination, and this showed that the ESR was 8 mm in an hour; the antistreptolysin titre (AST) was 280 IU per ml; the antistaphylococcal titre (ASTa) was 4.0 IU per ml. In January 1957 she had had pain of a diffuse nature in the knee-joints. X-ray examination of the knee-

joints had been normal. The clinical symptoms had gradually disappeared but had recurred at the end of the same year, when she also had begun to notice a hard tender swelling below the right knee. On this occasion, too, her toe-joints had been painful. She was first examined in the OPD of the Samaritan Children's Hospital (I. Bjelkhagen), and was found to have raised serum-cholesterol. Together with her younger sister she was admitted to the Hospital for investigation because of suspected essential hypercholesterolemia of a familial type. Clinical examination on admission showed no abnormalities except for a hard, non-movable, slightly tender mass, the size of half a hazel-nut, over the tuberosity of the right tibia. There was a suggestion of a similar mass in the same region on the left side. X-ray examination of the knee-joints (H. Gladnikoff) showed some streaky "calcifications" in the soft tissues in the region of the tuberosity of the tibia of the right leg. There were no other skeletal changes. X-ray of the chest was normal.

On March 25, 1958, examination of the heart and of the working-capacity was performed at the Infectious Diseases Hospital by E. Bengtsson. ECG at rest and on exertion was normal. Test in the upright position was normal for pulse-rate but not with respect to ECG findings. Phonocardiogram showed at the base a high-frequency systolic murmur of functional appearance. Working-capacity was low in relation to age, body-weight and heart-volume, but fell within the 95% range of standard error of a normal population. The heart-volume was normal in relation to body-weight. Hb 13.3 g/100 ml; red-cell count 4,500,000. The ESR was normal. Thymol turbidity 1. Alkaline phosphatase 13 Buch Units. Protein-bound iodine 5.7/100 ml. The serum-cholesterol level was raised (see Table 1 and Fig. 1). Glucose-tolerance curve was normal. Basal metabolism $+4\%$. The urine was normal.

Her weight on Jan. 3, 1958, was 38.8 kg; her height was 157 cm. On March 24 her weight was 39.9 kg, on May 23 41.0 kg; on Aug. 26 her weight was 42.8 kg and her

height 160 cm. She was on a normal diet with supplementary corn oil, 50 g daily, from March 10 to May 23, 1958.

Case 2. A girl, G.M., born on Aug. 3, 1948.—Except for a slight tendency to eczema she had been in good health. For a few weeks in January 1957 and in October 1957, she had complained of pain in the heels. There had possibly been some swelling of the Achilles tendon of the left foot during the latter period. Examinations at the OPD and in the Hospital in 1957 and 1958 showed no abnormalities. There were no signs of xanthomatosis. X-ray of the chest (H. Gladnikoff) was normal.

On March 25, 1958, ECG at rest and on exertion showed no abnormalities. Tests in the upright position were normal. Phonocardiogram showed a high-frequency systolic murmur, though with small vibration amplitude. The heart-volume was normal in relation to body-weight (E. Bengtsson). Hb 12.7 g/100 ml; red-cell count 4,300,000. The ESR was normal. Thymol turbidity 1. Alkaline phosphatase 10 Buch Units. The serum-cholesterol level was raised (see Table 1 and Fig. 1). Protein-bound iodine 6.4 μ /100 ml. Glucose-tolerance curve was normal. Basal metabolism $+10\%$.

Her weight on Jan. 3, 1958, was 33.3 kg; on March 24 her weight was 33.8 kg and her height 148 cm; on May 23 her weight was 34.5 kg; on Aug. 26, 1958, her weight was 36.5 kg and her height 149 cm. She was on a normal diet with supplementary corn oil, 50 g daily, from March 10 to May 23, 1958.

Case 3. J.M., born on April 18, 1918.—The patient was the mother of the two sisters, L.M. and G.M. She had begun to have joint trouble in 1951. In 1951 and 1952 she had been admitted to hospital on the diagnosis of rheumatoid arthritis. Corneal arcus, xanthelasma palpebrum, and xanthomas over the extensor tendons of the hands and the Achilles tendons had gradually developed. Microscopical examination of tissue from the latter region showed abundant cholesterol deposition. ECG in the

Fig.

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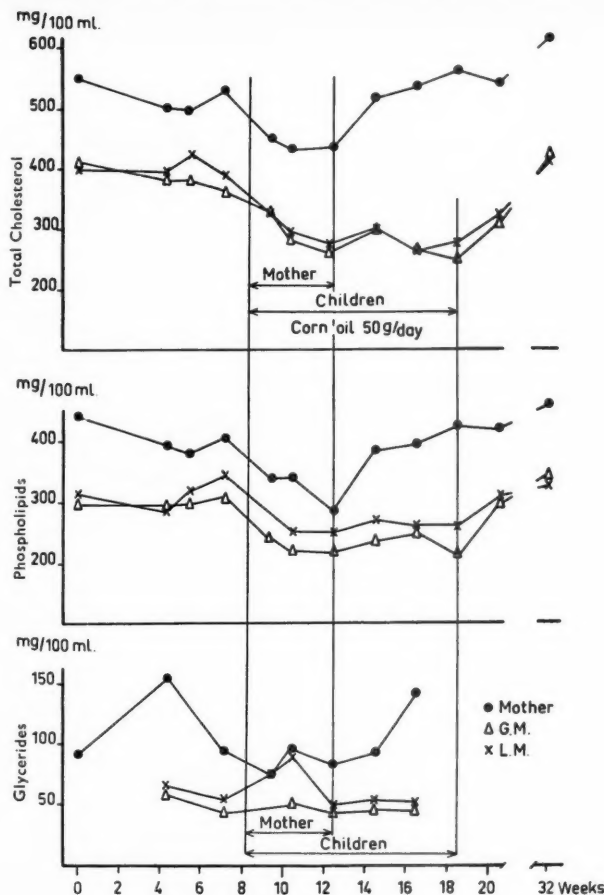


Fig. 1. The levels of total cholesterol, phospholipids and glycerides in the mother and the two sisters before during and after supplying corn oil to their food.

standard leads showed no abnormalities. There was no subjective heart trouble. Serum-cholesterol in October 1957 was 450 mg/100 ml (S. Aleman). Later estimations done by us showed also raised serum-cholesterol (see Table 1 and Fig. 1). The ESR was on several occasions about 30–40 mm in an hour. In March 1958 thymol turbidity 2 and alkaline phosphatase 2 Bush Units.

Her weight on April 9, 1958, was 55.7 kg

and her height 163 cm. On April 25 her weight was 54.3 kg. She was on a normal diet with supplementary corn oil, 50 g daily, from March 10 to April 11, 1958.

Methods

Blood was collected by venepuncture with the patients fasting. Serum was analysed for total cholesterol by the method of Sperry & Webb (18), for glycerides by the method

of Carlson & Wadström (5). The serum-lipoproteins were fractionated by Carlson's (4) technique.

Results

It will be seen from the table that the father had normal values for blood-lipoids, while the mother and both daughters exhibited a spectrum typical of essential hypercholesterolaemia with raised cholesterol levels and normal glycerides. Several analyses for lipoids were done (see Fig. 1) before corn oil was added to the mother's and the children's diet, which before as well as during and after the trial period had the composition of a Swedish standard diet.

When the girls were given 50 g of corn oil daily, their serum-cholesterol levels fell from about 400 mg/100 ml to about 260–300 mg/100 ml. About three months after corn oil had been stopped the serum-cholesterol had again reached the initial level of about 400 mg/100 ml. The phospholipids followed on the whole the variations of the cholesterol. The glyceride level, on the other hand, did not change. In the mother the results were similar.

Discussion

Kinsell (9), in 1952, showed that the serum-cholesterol level was influenced in different directions by animal and vegetable fats. These studies have been followed by a number of other reports. Ahrens and his group (3), for instance, have shown that corn oil has a definitely depressing effect on cholesterol, which seems to be attributable to the content of unsaturated fatty acids. Our patients were throughout the trial period on a normally composed diet without any restrictions other than

those due to personal taste. During the corn-oil period a marked depression of serum-cholesterol was obtained. We soon found, however, that we could not get our patients to consume the prescribed daily amount of corn oil for any length of time. The corn oil was taken in a pure form, either *au naturel* or as salad dressing. Both the mother and the children gradually became highly reluctant to further medication and this was discontinued on their own initiative.

Now that artificial dairy products (milk, cheese, margarine, ice-cream), in which the milk fat has been replaced by corn oil, have become available, we have advised our family to change over to a prophylactic diet composed as recommended by, for instance, Malmros (12) in cases of essential hypercholesterolaemia with or without xanthomatosis. Animal fat in the form of butter, cream, milk, cheese, eggs, pork and other fatty meat, as well as margarine and coconut fat are excluded from the diet and replaced by the above-mentioned artificial dairy products containing corn oil. The diet also includes vegetables, potatoes and other roots, fruit, fruit-juice, sugar, porridge, and bread (excluding white bread or cakes made with butter or coconut fat). Fish in free quantities is also allowed.

Since there are some animal experiments and other observations in support of the idea that dietary treatment as outlined above may be of value, and since the prognosis in children with essential hypercholesterolaemia seems to be extremely dubious, judging from the literature, attempts at such a change in the diet should be especially justifiable in these cases.

The question whether, on the whole, the morbidity in arteriosclerosis will fall, if the cholesterol can be maintained at a lower level for prolonged periods cannot, however, be answered at this early stage.

Summary

A family of four members is described. The mother and two daughters, 10 and 9 years old, had essential hypercholesterolaemia, the mother and the 10 year old daughter with xanthomatous changes.

Complete lipid analyses were done and showed high levels of cholesterol and phospholipids, and normal amounts of glycerides. During a period of normal diet 50 g of corn oil daily was given to the mother and the two daughters. A marked lowering of the cholesterol and phospholipid levels was obtained, while the glyceride content remained unchanged.

Xanthomatous lesions in children with

essential hypercholesterolaemia seem to be uncommon, and according to published reports such cases terminate in early death from heart disease.

Prophylactic dietary treatment with exclusion of certain animal fats and with the use of corn oil in the form of artificial dairy products is therefore to be considered indicated in children with familial essential hypercholesterolaemia, although the value of such prophylactic treatment is still uncertain.

Acknowledgement

We wish to thank dr. S. Aleman and dr. I. Bjelkhagen, who were responsible for the initial care of this family, for permission to study their cases. We are also indebted to docent E. Bengtsson for valuable help with the cardiac investigations.

Hypercholestérolémie essentielle chez deux sœurs. Effet de l'huile de maïs sur les lipides du sérum.

Description d'une famille de quatre personnes. La mère et deux filles âgées de 10 et 9 ans présentent une hypercholestérolémie essentielle, accompagnée pour la mère et la fille de dix ans de changement xanthomateux. Des analyses complètes de lipides furent faites et montrèrent un taux élevé de cholestérol et de phospholipides et des quantités normales de glycérides. Pendant une période de régime normal, 50 g d'huile de maïs furent administrés journellement à la mère et aux deux filles. Un abaissement marqué des taux de cholestérol, et de phospholipides fut enregistré, tandis que les quantités de glycérides restaient inchangées. La valeur d'un tel traitement prophylactique à base d'huile de maïs pour l'hypercholestérolémie chez les enfants est incertaine.

Essentielle Hypercholesterinämie bei zwei Geschwister. Wirkung von Maisöl auf Serumlipide

Es wird eine vierköpfige Familie beschrieben. Die Mutter und zwei Töchter, 10 und 9 Jahre alt, litten an einer essentiellen Hypercholesterinämie, die Mutter und die 10jährige Tochter mit xanthomatösen Veränderungen. Es wurde eine vollständige Lipidanalyse durchgeführt, und dabei erhöhte Spiegel von Cholesterol und Phos-

pholipoiden, sowie eine normale Menge von Glyceriden, festgestellt. Während einer gewissen Zeit mit normaler Diät bekamen die Mutter und beide Töchter täglich 50 g Maisöl. Es wurde ein beachtliches Absinken der Cholesterol- und Phospholipoidspiegel erreicht, während der Glyceridgehalt unverändert blieb. Der Wert solcher einer prophylaktischen Behandlung mit Maisöl bei einer Hypercholesterinämie der Kinder ist noch unsicher.

Hipercolesteremia esencial en dos hermanos. Efecto del aceite de maíz sobre los serolipidos

Se describe una familia de cuatro miembros. La madre y dos hijas, de 10 y 9 años de edad, sufrían una hipercolesteremia esencial, la madre y la hija de 10 años con modificaciones xantomatosas. Se hicieron análisis completos de los lípidos, comprobándose elevados niveles de colesterol y fosfolípidos, así como cantidades normales de glicéridos. Durante un período de dieta normal, se administraron a la madre y a las dos hijas 50 g diarios de aceite de maíz. Se obtuvo un descenso marcado de los niveles de colesterol y fosfolípidos, mientras que el contenido en glicéridos siguió invariable. El valor de este tratamiento profiláctico con aceite de maíz, en la hipercolesteremia de los niños, es aún incierto.

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CASE REPORTS

The Problem of Familial Multilocular Encephalomalacia

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The condition in which the brain of newborn infants undergoes rapid and extensive cystic degeneration has been described under many different names, such as "multilocular encephalomalacia", "multilocular cystic encephalopathy of infants", "progressive degenerative encephalopathy" and "polyporencephaly" (Kramer, 1956). The usual clinical picture is of neonatal distress, asphyxia, failure to thrive, convulsive movements, paralysis, unconsciousness and early death. At autopsy, the brain shows widespread, frequently symmetrical cavitation. The solid tissue surrounding the cavities presents evidence of myelin breakdown, neuronal loss, glial proliferation and phagocytosis of neutral fat. This condition is probably due to different, still unknown, causes and one of us recently considered its association with vascular lesions of possible thrombotic origin (Crome). Whatever the cause, the morphological similarity of the process suggests the action of certain common pathogenetic mechanisms (Lumsden).

Multilocular encephalomalacia has often been discussed in relation to "demyelinating disease", namely, swayback in lambs and human diffuse sclerosis. In the group of conditions, formerly known collectively as Schilder's disease or diffuse sclerosis,

the one most closely resembling multilocular encephalomalacia is Krabbe's infantile diffuse sclerosis (Krabbe; Russel & Tallerman). This disease is now more commonly referred to as infantile leucodystrophy, since the original group of the diffuse sclerosis is thought to include at least 3 different diseases: infantile or juvenile forms of disseminated sclerosis, sclerosing leuco-encephalitis, and leucodystrophy (Poser & Bogaert).

The morphological similarity of multilocular encephalomalacia to swayback is indeed striking, but comparison with leucodystrophy shows differences. Leucodystrophy, unlike multilocular encephalomalacia, is often familial with evidence of recessive inheritance, and there is usually a clearly distinguishable period of normal development between birth and the onset of the disease. Morphologically, cavitation is less and fibrous gliosis more marked in leucodystrophy, the brunt of the lesions being borne by the white matter, and the subarcuate myelin fibres and the cortex being often spared. It is therefore possible to distinguish typical cases of the 2 conditions from each other, although none of the above criteria is absolute. In very young infants it is often impossible to be certain of normal health and development

before the onset of the symptoms, whilst, pathologically, marked cortical involvement as well as extensive cavitation have often been reported in cases of leucodystrophy. However, familial occurrence of multilocular encephalomalacia has hitherto not been established, although the 2 cases presented by Kramer had relatives affected by different neurological diseases. It is therefore worthwhile recording the following 2 cases of encephalopathy in siblings. One of these is still alive, having microcephaly, spastic paralysis and idiocy; the other has come to autopsy presenting typical features of multilocular encephalomalacia.

Case 1. W.F.

The parents are in good health and not related by blood. The mother has had 4 pregnancies. The first and fourth of these gave rise to the two cases described below. The second pregnancy ended at 8 weeks in a spontaneous abortion. The third child was a normal healthy boy who is now in his fourth year. There is no other significant family history.

The first stage of labour lasted 68 and the second $1\frac{1}{2}$ hours. Meconium was passed but the foetal heart remained strong. The head was delivered fairly easily with forceps. The birth weight was 3200 g. The baby was shocked and was thought to have inhaled liquor amnii. Her respirations were rapid and shallow and continued so throughout the first day of her life; there was also evidence of leftsided spasticity. The fontanelles were not tense. Six days later she was said to be "like a case of cerebral oedema". Thereafter she was an inactive lethargic baby who cried infrequently and was very difficult to feed. The head circumference at birth was not noted.

On admission to this Hospital, aged 13 months, all limbs were grossly hypertonic. The tendon jerks were markedly exaggerated, the abdominal reflexes were absent,

there was sustained ankle clonus and her plantar reflexes were extensor. The head circumference was 41.9 cm, the norm for this age and sex given by Westropp & Barber being 45.6 cm, S.D. = 1.22.

Her optic discs were atrophic but she followed a light. She showed some response to sound, but her general level was that of an idiot. She is now $5\frac{1}{2}$ years old and remains of idiot level, with a spastic diplegia. Her eyes no longer follow a light and she makes no response to sounds. Her head circumference is 46.5 cm. The norm for her age and sex is 51.2 cm, S.D. = 1.50 cm, so that her head circumference is more than 3 S.D. below the mean. It is our practice to describe such cases as microcephalic. She is extremely small for her age, weighing only 12,300 g. Though her head is very small, it is not markedly disproportionate to the rest of her body and her facial features are symmetrical and neat. Until the birth of her younger sister, it was thought that her condition resulted from anoxia or other birth injury.

An EEG at $5\frac{1}{2}$ years was interpreted by Dr. J. Foley as follows:—"The EEG is abnormal. In the posterior parts of the hemispheres there is irregular low voltage activity at 5 and about 2-a-second. More anteriorly, the 5-a-second activity is of higher voltage, and is more rhythmic, though it is often disturbed by high voltage slow activity at about 1-a-second, and also by occasional rhythmic low voltage 8-a-second activity. The record suggests brain damage predominantly in the frontal areas".

The same general features were seen in another EEG taken 2 months later.

The X-ray report (Dr. R. L. Quillam) stated: "The skull is relatively small and asymmetric. There is an upward convexity of the anterior fossa. A metopic suture appears to be present. There is no evidence of intracerebral calcification."

Case 2. A.F.

This girl was born when the father was 38 and mother 36 years old. Presentation was by vertex, R.O.A., the first stage of labour

lasting 9 hours 40 minutes, and the second—5 minutes. The placenta was normal. The baby weighed 3500 g and was in a state of white asphyxia. Thick mucus in the air passages was difficult to aspirate. She was given intragastric oxygen, lobeline gr. 1/20, "synkavit" (vit.K) 10 mg, and "achromycin" (tetracycline) twice daily for the first few days. The head was not measured.

Her hold on life remained precarious until death a month later. She was unconscious, her limbs lacked tone, the knee jerks were brisk and she was reported once to have had convulsive movements. Her temperature rose on a few occasions to 38.9°C but most of the time she remained hypothermic.

Laboratory investigations on the first day (Dr. J. K. Carter) were as follows:—*C.S.F.* yellowish fluid under normal pressure with protein 120 mg/100 ml, no raised globulin, sugar 53 mg/100 ml, and 15 R.B.C.'s. *Blood urea*—48 mg/100 ml, and *blood sugar* by the Folin-Wu method was low—63 mg/100 ml. Her *serum sodium* was 290 mg/100 ml, i.e. 126 mEq/l, *serum potassium* did not exceed 21.8 mg/100 ml—i.e. 5.6 mEq/l, and *serum chloride* as Na Cl—555 mg/100 ml, as Cl—340 mg/100 ml, i.e. 95 mEq/l. With the methods used the sodium was slightly low

and the chlorides normal. *The alkali reserve* (CO_2 combining power) was extremely low—27.4 vols. per cent, i.e. 12.2 mEq/l. These findings were thought to indicate severe acidosis, although respiratory alkalosis (primary CO_2 deficit), due to hyperventilation could not be excluded on the data available. The biochemical examination of the urine was done on the 9th day (Dr. W. W. Kay) at the Mental Hospitals Group Laboratory, West Park, Epsom, by the Norymberski technique. The *urine ketosteroids* were 0.05 mg/6 hrs, *creatinine*—0.17 g/6 hrs, *urine volume*—12 ml/6 hrs, and *total corticoids*—0.26 mg/6 hrs.

An *X-ray* of the skull showed no evidence of toxoplasmosis. The mother's toxoplasmin dye and complement fixation tests were positive; the patient's negative. *Haemoglobin* at 14 days was 162 per cent (Haldane) or 23.98 g/100 ml.

Pathological findings

The brain weighed 210 g (average normal for age—413 g). It was symmetrical, soft and fluctuant. The position and number of gyri was probably normal, although it was difficult to be certain of this on account of



Fig. 1. Coronal section through right cerebral hemisphere. Heidenhain stain.

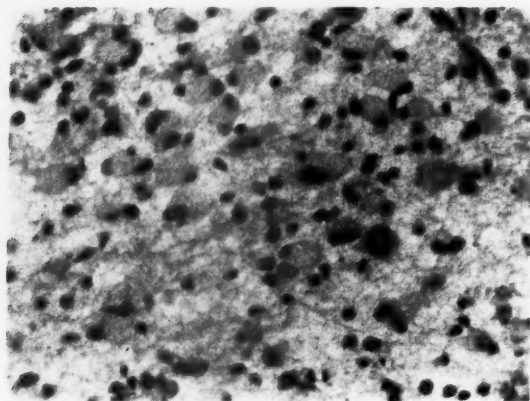


Fig. 2. Glial hyperplasia of cerebral cortex. H. and E. $\times 500$.

partial collapse and flattening of the cortex. The cut surface showed that the entire brain tissue had largely disappeared under the thin and partially torn shell of the remaining cortex, leaving only a central core of solid matter in the position of the basal ganglia (Fig. 1). Many cavities containing slightly cloudy colourless fluid occupied the intervening space. The cavities were incompletely separated from each other by gelatinous septa and web-like trabeculae extending towards the surface from the solid tissue of the basal ganglia. The basal ganglia contained a large number of small cysts and showed no recognisable nuclear structure. The ventricles were not dilated. The corpus callosum was thin, greyish in colour and somewhat gelatinous in consistency.

The cerebellum was small, weighing together with the brain-stem 18 g. (This is about half of the average normal weight for her age, from our unpublished observations.) It showed no cavitation on the cut surface, but the dentate and roof nuclei could not be identified. The cerebellar cortex was simplified, showing few ramifications of the arbor vitae and absence of the usually clear demarcation between grey and white matter.

The brain-stem was firm in consistency, showed no cavitation, but its nuclear structure was barely discernible.

After prolonged fixation in formalin most of the brain was cut in coronal blocks and these were embedded, together with representative portions of the brain-stem and cerebellum, in paraffin and in celloidin. Sections were stained by the customary general and neuro-histological methods, frozen sectioning as well as gelatin embedding being employed for myelin staining and for silver impregnation.

The blood vessels and meninges were normal, but a few fat-laden phagocytes were present in the subarachnoid space.

The extent of cortical destruction varied from area to area. The cortex was preserved in its entire thickness in only a few places; elsewhere all the deeper layer had been destroyed, and the rim consisted mostly of little more than the molecular layer. Nerve cells were present in the better preserved areas showing in a few places a surprisingly normal type of lamination. Elsewhere, however, the cortex was formed almost exclusively by proliferated glial cells (Fig. 2). These were, as elsewhere throughout the brain, of 2 kinds: swollen-bodied astrocytes ("gemästete Zellen") and microglial compound granular corpuscles. Both contained sudanophilic material, so that the entire affected area seemed filled with red particles in the Sudan preparations (Fig. 3). In the

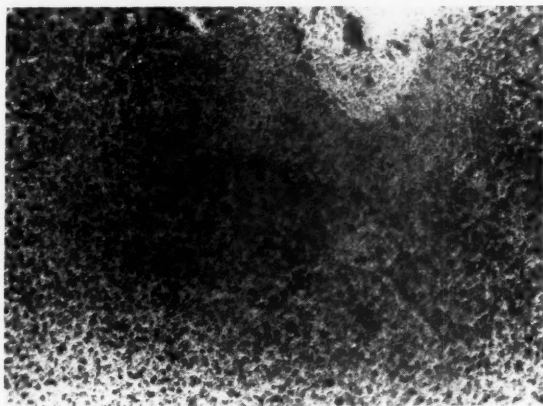


Fig. 3. Cerebral cortex. Herxheimer's Scarlet R. $\times 100$.

astrocytes the fat was in the form of fine granules arranged around the periphery of the cells, the central mass of the cytoplasm staining a homogeneous pale yellow or orange. The compound granular corpuscles were fully laden with coarse particles of brightly staining fat. A striking feature was the preservation, in a fully calcified state, of many nerve cells and their processes in the deeper and otherwise gliosed and rarefied portions of the cortex (Fig. 4). These stained darkly with haematoxylin and were positive

by the von Kossa method. Apart from the few calcified processes of these cells, no myelin fibres could be seen in the cortex or degenerated white matter of the centrum semiovale.

The web-like remnants of gelatinous tissue extending between the basal ganglia and the cortex were also formed by astrocytes and microglia.

The basal ganglia showed better preservation than the cortex, though few of their nuclear formations could be identified with

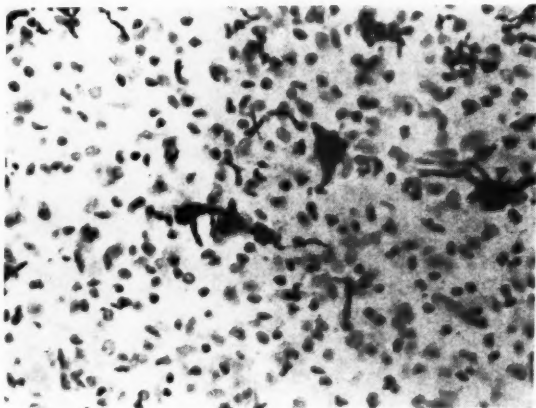


Fig. 4. Calcified nerve cells in cerebral cortex. Von Kossa $\times 500$.

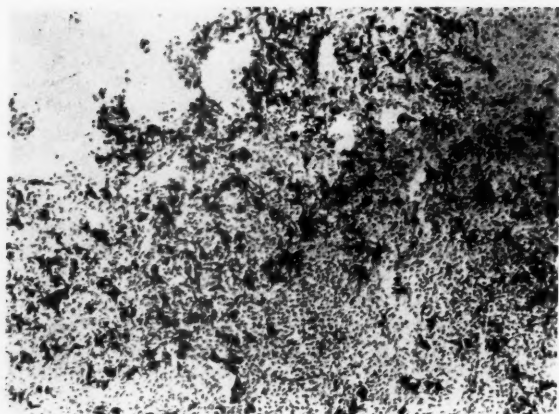


Fig. 5. Calcified nerve cells in the thalamus. Von Kossa $\times 100$.

certainty. Calcification of many nerve cells was even more striking here than in the cortex (Fig. 5) and this was associated with calcification of entire bundles of nerve fibres (Fig. 6). Myelin was also better preserved

in the basal ganglia, many of the larger tracts being identifiable, although all showed some degeneration when viewed under higher magnification. The small cavities, seen macroscopically, were filled by many fat

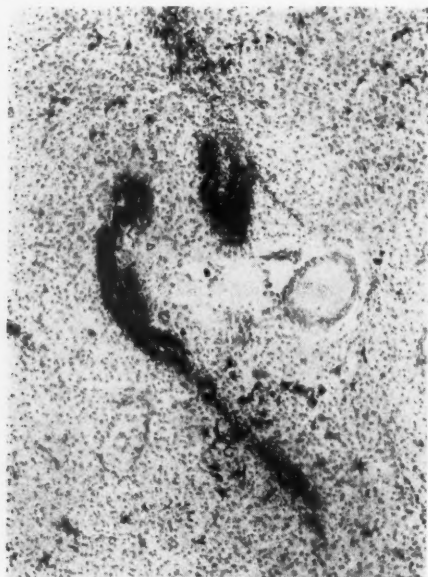


Fig. 6. Calcified nerve tracts in basal ganglia. Von Kossa $\times 100$.



Fig. 7. Perivascular cuffing with phagocytic cells in the thalamus. H. and E. $\times 100$.

Fig. 8.

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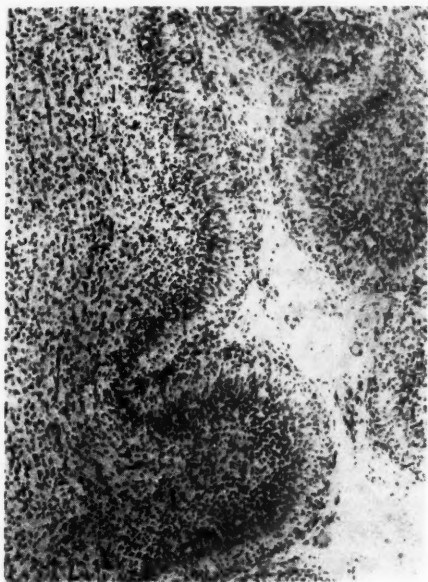


Fig. 8. Cerebellar cortex showing proliferation of Bergmann glia and atrophy of molecular and granular layers. Cresyl violet $\times 100$.

laden phagocytes and fluid. In the solid tissue the process of degeneration appeared to be more recent; some areas of dense microglial proliferation alternating with others showing perivascular cuffing by similar cells (Fig. 7). The ependymal lining of the ventricles was frequently denuded, and the periventricular solid tissue showed marked astrocytic proliferation.

In contrast to the marked cellular glial hyperplasia, fibrous gliosis was difficult to demonstrate, only a few areas showing a delicate reticulum of glial fibres when stained by the Holzer method.

The brain-stem presented diffuse and uniform astrocytic hyperplasia but no cavitation. There was much neuronal loss in all nuclear formations, the inferior olives, in particular, being scarcely recognisable. The pyramids did not stain for myelin. The other fibre tracts, did so, albeit imperfectly.

The sulci of the cerebellum were shallow. The superficial granular layer was present,

consistent with the age of the subject. The subjuncting molecular layer was very narrow, being entirely absent in some places. Only few widely scattered Purkinje cells were identifiable and their usual position was marked by stratified cells of Bergmann glia type (Fig. 8). The granular layer showed marked cellular depletion. The myelin stained poorly in the white matter of the cerebellum, few nerve cells could be seen in any of its nuclear formations and there was, as elsewhere, considerable astrocytic proliferation.

Staining for iron was negative throughout the brain.

The only non-neural abnormality recorded in the autopsy notes was basal congestion of the lungs.

Discussion

The clinical and pathological findings in Case 2 are quite characteristic of multilo-

TABLE 1. *Three cases of microcephaly whose head circumference at birth was within normal limits.*

Name and sex	Birth weight	Head circumference at birth	Head circumference		Normal head circumference for age and sex in		Birth and neonatal history	Neurologist's report
			age	cm	cm	S.D.		
S.G. F.	3200g	"normal"	3	41.5	49.5	± 1.35	L.O.P. presentation. Considerable traction with forceps. Appeared normal at 1 mth. Legally adopted at 4 months.	Blind. Spastic diplegia.? failure of myelination.? birth injury.
A.A. M.	3300g	31.7 cm	3	42.5	50.4	± 1.35	Spontaneous birth. Spasticity noted at 7 months.	Coloboma of chloroid. Generalized rigidity. Prenatal damage suspected.
G.H. M.	3600g	36.2 cm	2½	44.5	49.8	± 1.39	Occipito-posterior presentation. 2nd st. 2½ hours. Limp at birth and had 3 fits. Appeared normal at 6 weeks.	"Motor phenomena are those of the new born infant . . . mediated entirely by brain stem reflexes."

cular encephalomalacia. The amount of cerebral destruction had reached a very advanced stage at the time of death, possibly signifying the relative success of the measures taken to maintain life despite the gravity of the disease. Calcification of nerve cells and their processes is well known in cases of cerebral cavitation and gliosis. There were no traces of haemorrhage or trauma, and the cerebellar dysgenesis suggested prenatal onset of the disease.

The brain of Case 2 was small but there was no definite evidence of corresponding smallness of the head—microcephaly, before death at 1 month. It may be thought that normal head size in one and microcephaly in another sibling excluded common disease. This is not necessarily so.

For example, out of 45 mentally defective children in one ward of this Hospital, there are 3 whose head circumference was normal at birth but who are now microcephalic (Table 1). Hence, definite microcephaly might have become evident in Case 2 had the patient lived long enough. However, it remains uncertain whether the disease in the 2 siblings is identical. In Case 1 it may have been due to birth injury, as suggested by the history, or to some prenatal cause unrelated to multilocular encephalomalacia.

On the other hand, the possibility of an identical disease, i.e. multilocular encephalomalacia, must also be considered. Although it is generally thought that the condition is rapidly fatal, this opinion may have been formed by accumulation of

publications dealing only with cases coming to autopsy; it is almost impossible to confirm the diagnosis in living infants. Analogy with swayback, which this disease so closely resembles, suggests that some of the patients may recover. Thus, it is known that some of the lambs may survive early illness (Innes & Shearer). Moreover, the amount of cerebral destruction in affected lambs is inconstant (Barlow), some showing no gross cerebral lesions. In the experience of Barlow (personal communication), milder cases of swayback which had come to autopsy aged up to 10 months showed no cerebral lesions of any kind, and their brain-stems and spinal cords also appeared normal. Hence, it seems impossible, if the analogy may be pursued so far, to exclude occasional occurrence of non-fatal multilocular encephalomalacia, and Case 1 above could be tentatively regarded as an example of this disease.

Summary

Severe encephalopathy is reported in 2 siblings. One has come to autopsy, aged 1 month, presenting the typical feature of multilocular encephalomalacia. The other is alive, being 6 years old and suffering from microcephaly, spastic diplegia and idiocy. The possibility of the occurrence of non-fatal familial instances of multilocular encephalomalacia is considered.

Acknowledgements

We are glad to acknowledge help received from our colleagues. Dr. J. Burkinshaw has placed the clinical notes, and Dr. S. T. Allen the brain of Case 2 at our disposal. Miss M. F. Craib investigated the social background of the family. Drs. J. Foley and R. L. Quilliam have helped in the investigations of Case 1. The chemical investigations were made by Dr. J. K. Carter and Dr. W. W. Kay.

Problème de l'encéphalomalacie multiloculaire familiale

Deux frères présentent des cas graves d'encéphalopathie. On trouve à l'autopsie chez l'un d'eux âgé d'un mois les caractéristiques typiques d'une encéphalomalacie multiloculaire. Le deuxième frère est en vie, âgé de six ans atteint de microcéphalie, de diplegie cérébrale et d'idiotie. On considère la possibilité de cas familiaux d'encéphalomalacie multiloculaire non mortelle.

Das Problem der familiären multilokulären Enzephalomalazie

Es wird über eine schwere Enzephalomalazie bei 2 Geschwistern berichtet. Bei einem wurde im Alter von 1 Monat eine Autopsie vorgenom-

men, wobei sich das typische Bild einer multilokulären Enzephalomalazie ergab. Das andere Geschwisterteil lebt, ist 6 Jahre alt und leidet an Mikrozephalie, spastischer Diplegie und Idiotie. Die Möglichkeit des Vorkommens von nicht letalen familiären Fällen multilokulärer Enzephalomalazie wird in Betracht gezogen.

El problema de la encefalomalacia multilocular familiar

Se informa sobre una grave encefalopatía en 2 hermanos. Uno ha sido sometido a autopsia a la edad de 1 mes, presentando el cuadro típico de una encefalomalacia multilocular. El otro vive, tiene 6 años y padece microcefalia, diplegia espástica e idiotéz. Se considera la posibilidad de que sobrevengan casos familiares no fatales de encefalomalacia multilocular.

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CASE REPORT

Cold Urticaria

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Among the forms of urticaria caused by physical agents, cold urticaria seems to be the most common (5, 20). Different types of reaction to cold have been described: first, localized or general urticaria and, second, urticaria accompanied by various types of systemic manifestations (7, 8, 14). In dermatological practice, patients with cold urticaria seem to be met with fairly often (12, 17). In children, the disease must be rare—only 5 cases have been found in the literature on the subject (1, 6, 9).

The pathogenesis probably varies from one case to another, and no uniform explanation can be obtained from the literature (8, 13, 14, 18, 20). To sum up, it may be said that cold urticaria is found both of allergic and of non-allergic origin. Several writers (7, 8) have supposed that the essential fact in the pathogenesis is the liberation of a histamine-like substance, possibly histamine itself. In such cases, either the skin would be especially hypersensitive to histamine or else the amount liberated would be so great that a super-normal reaction followed. Some 20 years ago, Horton *et al.* (7) gave an account of 22 cases from the Mayo Clinic where, in

several cases, they had succeeded in developing exactly the same symptoms in the patients by the injection of histamine as on exposure to cold.

In a number of cases, some other liberating agent besides the chill seems to have been required. Thus, for example, the case is reported (9) of three sisters aged 8 to 13 years who, after measles, developed a cold urticaria of duration 6 months to 1 year. Herlitz (6) has described a 15-month-old girl in whom the typical reaction could only be produced during the time the girl was receiving daily supplies of a special type of throat pastille. Other cases of nutritional allergy have also been reported.

Case Report

A 10-year-old girl was admitted into KLB in September 1958 with a history of illness covering some months. In her family, asthma bronchiale was found in two of her mother's adult relatives. The girl herself had never shown any allergic manifestations. In earlier years she had been fairly sensitive to infection, but a considerable improvement had taken place in recent years. In 1951 she appears to have had varicella (medical diagnosis and secondary cases in the neighbourhood). The

patient fell ill again in April 1958, however, with what seems to have been typical varicella. In the girl's class at school there were several others ill with chicken-pox at the same time. After two weeks the patient was fully recovered, but some weeks later it was noticed that she complained of itching and felt cold. It was observed also that reddened swellings came up here and there on the body. These were very transient but the trouble showed no tendency to decrease. By degrees it was noticed that the symptoms appeared only when the girl was out of doors. In May 1958 she was put on a diet, which had no effect whatever upon the symptoms. During the summer, she could not bathe or go barelegged on account of the subjective troubles experienced.

The patient was somatically and psychically normally developed. The skin was generally somewhat dry, no obvious dermatographia. No sign of infection present. No cold haemoglobinuria. Normal blood values, slight eosinophilia. No sign of haemolysis. Coombs's test, WR, cold agglutination-negative. Cholesterol 196 mg %. Electrophoresis-no comment. Urine content normal. Normal daily evacuation of corticosteroids and 17-ketosteroids. ACTH-test with patient in bed-nothing to report. BMB -2 %, -10 %. Glucose tolerance test, EEG and ECG-nothing to report.

The patient reacted with urticaria and localized oedema on exposure to cold in the form of cold wind and cold water. No general phenomena were found; pulse and blood-pressure-nothing to report. With oral chilling, through eating ice-cream-no definite reaction. The temperature limit at which urticaria appeared was difficult to establish exactly, but lay in the region of 18°C. For example, the patient showed the symptoms in the mornings when she held her hand outside the warmth of the bed. The amount of the fall in temperature affected the degree of severity of the symptoms, which were more troublesome with a big difference in temperature. An odd phenomenon was that peripheral cooling, which produced redness and urticaria, went in the form of streaks

from the periphery, like a lymphangitis. A further observation made was that central stasis of the exposed arm could prevent the extension of the urticaria to other parts of the body. The patient was subjected to a strict elimination diet, but no nutritional allergy could be shown. Complete intracutaneous test negative. The histamine reaction was normal as was also the skin reaction to acetylcholine and adrenalin i.e. Passive transfer test (Prausnitz-Küstner) was carried out with three different control persons. Result completely negative. Exposure to cold gave a quantitative increase in the eosinophilic cells in the blood. This increase might have been restricted to some extent by the ACTH or Iergigan i.m. given before exposure. No definite decrease in the urticaria was perceived, however. The basophilic cells counted in 2000 white ones showed no difference before and after exposure to cold. Leucocytes, lymphocytes and thrombocytes showed no distinct change either.

Therapeutic efforts were made with 6 different types of antihistamines:

1. Antazolin (antasten, Ciba)
2. Prometazin (Iergigan, Reicp)
3. Phenindamin (thephorin, Roche)
4. Calcium lactobionate + thenophenopiridin (Ca-Sandosten, Sandoz)
5. Chlorecyclizin (trihistan, Kabi)
6. Diphenhydramin (desentol, Leo),

3 types of steroids (cortisone, prednisolon, triamecinolon), and atropine. In addition, histamine hyposensitization was carried out by daily doses of up to 2 ml s.c. during 2 different periods of 3 weeks. Cold hyposensitization was tested for a month by two 5-minute handbaths daily with successive lowering of the temperature to +2°C. None of these measures led to any result whatever.

The girl's subjective troubles were still expressed partly in the form of itching, sensation of swelling and aches, partly also in a psychic form. In fact, the urticaria was often so extensive that people living in the neighbourhood believed her to be suffering from some contagious disease.

Discussion

The "lymphangitis phenomenon", earlier reported in rare cases (7 and 14), might be explained by a liberated substance being carried along the lymph vessels. That it is really a question of a substance in circulation is supported by the observation made during stasis. This phenomenon seems to occur in practically every case of cold urticaria (8). It has long been known that histamine is an important factor in allergic manifestations, but in spite of that there is sparse evidence of increased production of histamine in such conditions (2). As a case of this sort seemed very suitable for histamine analyses under various experimental conditions, we have attempted to have these performed. Thanks to the co-operation of Dunér & Pernow, and using a method described by them (3), we have been able to carry out both blood and urine analyses of this patient. A considerable increase in the histamine content of both blood and urine on exposure to cold was thereby established. It appears to be one of the few cases in man where it has been possible to show this by reliable methods of histamine-determination (15). The significance of this discovery has been taken up for further investigation (4).

The correlation between absolute or relative figures for various blood constituents and the histamine-content of blood and urine has fluctuated a great deal in the present case. Unfortunately, the experimental investigations in respect of this patient could not be taken far enough to produce any significant values. The data in this field reported in the literature on the subject are also quite divergent (2, 11),

which renders estimation of the results more difficult.

The etiology and pathogenesis in the case described here are particularly obscure. The accuracy of the anamnesis concerning varicella might be impossible to check, but it must, of course, be treated with considerable suspicion. It is clear, however, from other cases also that virus infections (9) or bacterial foci (12) may be liberating factors. In spite of the unsuccessful passive transfer test—although the test is unsuccessful in more than half the cases of cold urticaria (8, 19)—one can perhaps count in this case, too, on an antigen-antibody reaction as the primary cause. How complex (and to a large degree still unknown) the "allergic reaction" is, is shown with all clearness by the survey recently issued from the Mayo Clinic by Logan (10).

The therapeutic problems in cold urticaria cases are generally considerable. Various paths have been tried with very varying success, and when in addition one has to take into account spontaneous healing in a proportion of cases it is naturally difficult to estimate the results. "Cold hyposensitization" has proved effective more often than histamine hyposensitization (8). Antihistamines have been effective in exceptional cases (16) but have generally proved ineffective. Herlitz (5) obtained very good result with a 30-year-old woman by the use of atropine, and since this was used successfully by others (10) in the treatment of other types of urticaria we tried atropine in large doses on this girl. As with all the other attempts at treatment, the result was completely discouraging. The hope that corticosteroids, with their generally striking effect on

clinical manifestations of hypersensitivity (10, 11) might improve the patient's condition has unfortunately not been realized. Since the disease has now remained unchanged for 1 year, there seems little chance either of spontaneous healing.

Summary

The case of a 10-year-old girl with cold urticaria without systemic manifesta-

tions is described. The symptoms began after a probable recurrence of varicella. An important degree of physical and psychic trouble was found. Extensive laboratory analyses were completely negative. Observations made in connection with tests of exposure to cold are discussed. Increase of histamine in blood and urine in conjunction with exposure to cold has been established. Therapeutic attempts of various kinds have proved unsuccessful.

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Urinary Tract Infections

I. Drugs and Bugs in Urinary Tract Infection from the Bacteriological Point of view

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The pleomorphic nature of urinary tract infections presents the physician with an intriguing problem. As a group they are probably among the most common bacterial infections in hospital practice, but they are nevertheless often overlooked. On the other hand, what seems to be a clearent based on a "positive" culture, may turn out to be a faulty interpretation of laboratory findings. Finally, in spite of good immediate results after antimicrobial therapy, there is a remarkable tendency to chronicity, which makes it a long-term problem.

Optimal management of symptomatic urinary tract infections depends to a large extent on the precise identification of the infecting organism(s) and the determination of their antimicrobial susceptibility. In the frequent asymptomatic cases the situation is more complicated owing to the lack of correlation between the clinical picture and bacteriological findings. An isolated microbe must not prematurely be considered as a "contaminant". Repeated bacteriological examinations are consequently of even greater importance in these cases.

Urine is usually an excellent culture medium for the common pathogens of the urinary tract. Growth is still better in urine from patients with urinary infections and is further accelerated by slight alkalinity, glucose, or serum. Acidity and hypertonic saline have the opposite action (9). — If small numbers of bacteria are discharged from the kidney, they will multiply in 8-12 hours to about 10^6 bact./ml of urine in the bladder or elsewhere (12). Since the urethra of a normal person is far from being a sterile canal (2, 6) it is obvious, that urine may be contaminated either when spontaneously voided or collected by a catheter; even a slight inoculation will result in a heavy growth if the sample is left for some hours. The flora usually consists of diptheroids avirulent staphylococci, *Strep. faecalis*, *Esch. coli*, and members of the *Proteus* group. A few can easily be classified as "contaminants", but the others may be pathogens since they are often isolated from proven cases of infection.

Consequently it can be inferred that the final interpretation of the bacteriological findings must depend on at least 3 factors:

- 1: Proper technique when collecting a urinary specimen.
- 2: Realizing the importance of what might be called the "time factor".
- 3: Proper distinction between "contamination" and "true" bacteriuria.

In boys a "midstream portion" can be accepted after thoroughly cleansing the meatus with soap and water followed by disinfection. Samples from girls usually have to be obtained by catheterization since the vulva can hardly be cleansed until free from bacteria. Furthermore, micturition pressure forces part of the urinary stream back through the lower parts of the vagina, where it gets contaminated in pre-adolescent girls. Only in pyuria, where the concentration of bact./ml of urine is above 10^5 , there is an acceptable correlation between voided and catheterized urine (10).

If the collected urine is not sent to the bacteriological department within a few hours, bacteria will either multiply or die. Depending on physico-chemical factors like temperature, pH, and organic materials present, the total number of microbes as well as their relative proportions may change rapidly. A sample, sent to the bacteriologist after some delay, may have been overgrown by an insignificant bacteria. Its identification and sensitivity pattern will not be relevant to the problem of therapeutic management. — It is therefore recommended that urinary specimens should be delivered to the laboratory within two hours after collection. If that is not possible, they should at least be kept in a refrigerator.

Even if the urine has been collected and cultivated under optimal conditions, the

presence of a "positive" culture does not prove without further control, that the bacteria actually are of etiological significance. Urine from normal persons often contains up to 100–500 bact./ml, largely from the urethral flora or unavoidable minimal contamination in the course of collection. Using the technique of so-called "quantitative cultures" many authors (12, 13, 14, 19, 22) consider it possible to differentiate between contamination and what has been termed true bacteriuria. The precise number of viable organisms/ml of urine which permits the diagnosis of true bacteriuria is not generally agreed upon, partly due to different techniques in collecting the samples. In recent papers, however, the range has been narrowed to 50,000–100,000 bact./ml (13, 19, 22). When in excess of these numbers, the diagnosis of a urinary tract infection is affirmed. Patients with fewer than 100,000 bact./ml in the freshly voided urine may require further observation, since about 5% of the patients with low bacterial counts actually have chronic pyelonephritis (10, 13).

Apart from the problem of interpretation, and perhaps of more sinister importance, is the question of possible iatrogenic implantation of bacteria into the urinary tract during diagnostic manipulations, e.g. catheterization of girls to collect urine samples. Such nosocomially inoculated organisms, often resistant hospital strains, may produce a serious disease. The incidence of symptomatic manifestations following single instrumentations, including catheterization and cystoscopy, has been reported as between 2–4% (2, 6, 12, 13, 14, 18). Asymptomatic cases are probably more frequent. — In any case

the risk of bladder catheterization must be realized and carefully weighed against the possibility of overlooking clinically inapparent infections (3). — At times a shaking chill after a lag period of 30–90 min, the "catheter fever", signals the sudden, transient influx of micro-organisms into the blood stream.

The use of prophylactic drugs to minimize the dangers inherent to instrumentalizations has been of little benefit (10), and consensus now seems to be that they should be avoided.

Management of urinary tract infections differs by necessity somewhat in general practice and in hospitals. A practitioner (G.P.), when called upon to treat a case of "cystitis", usually cannot base his treatment on bacteriological findings. Nevertheless he needs a working knowledge of the bacteria, which most frequently cause urinary infections in an unselected material. Table 1 gives both the causative organisms and their relative distribution as reported in an American material of about 1174 cases, most of them from general practice. This picture ought to be fairly representative of the situation outside hospitals in Sweden, too. — As can be seen, Gram-negative bacilli usually cause acute infections. The same is often true in exacerbations in chronic infections. In cases with smoldering, asymptomatic chronic infections, however, Gram-positive organisms are quite frequent. In uncomplicated infections a single species of bacteria is isolated in 80–100% as compared to about 20% in infections complicated by structural abnormalities (6, 12). — Basing therapy on this bacteriological fundament, the G.P. wants a drug which covers the spectrum

TABLE 1. *Causative microorganisms in 1174 cases of urinary infection.*

	cases	per cent of total
<i>Esch. coli</i>	450	46.39
<i>Str. faecalis</i>	192	19.79
<i>Ps. aeruginosa</i>	98	10.10
<i>Staph. albus</i> and <i>aureus</i>	61	6.28
<i>B. proteus</i>	57	5.87
<i>A. aerogenes</i>	48	4.94
<i>Mycobacterium tuberculosis</i>	25	2.67
<i>Gaffky tetragen</i>	13	1.34
<i>K. pneumoniae</i>	12	1.23
Hemolytic streptococci	4	0.41
<i>Neisseria catarrhalis</i>	4	0.41
<i>B. subtilis</i>	2	0.20
<i>Alcaligenes faecalis</i>	1	0.10
<i>Pneumococcus</i>	1	0.10
Multiple microorganisms*	204	17.37

* The combination of *Esch. coli* and enterococci occurred in 75 cases (6.47 per cent).

(From Rhoads P. S. Management of urinary tract infections. *Postgrad Med.* 21, 563, 1957.)

of the organisms most commonly encountered, and which at the same time has few side effects. At present, the first choice should perhaps be one of the highly soluble sulfonamide compounds, which often give favorable results and have proved themselves reasonably safe. While in vitro determinations of sensitivity against sulfonamides are notoriously unreliable, experience has shown, that *Esch. coli* is sensitive in about 90% of the cases, *Strep. faecalis* is naturally resistant, and staphylococci are increasingly resistant. — Of late sulfonamide mixtures with high solubility have appeared, but sufficiently detailed clinical studies have not yet been performed to permit adequate comparisons with single compounds. Nitrofurantoin may be a useful complement, especially in patients with a history of previous sulfonamide sensitivity. It is most active

against *Esch. coli*, of intermediate effect against *A. aerogenes*, and completely ineffective against *Pseudomonas*. In *Proteus* infections the results have been quite variable. — Penicillin, which is used now and then in urinary infections, is of little value as the commonest bacteria are resistant *a priori*.

In persistent infections or when relapses occur, the question of further antimicrobial therapy outside the hospital arises. Since about $\frac{3}{4}$ of all infections are complicated by obstructive lesions of the urinary tract, a therapeutic failure may be caused either by drug resistant organisms or predisposing structural abnormalities. To avoid the dangerous and timeconsuming selection of broad spectrum antibiotics by guesswork, the patient should be given the benefit of cooperation between the G.P. and his colleagues in a hospital.

Rational management and therapeutic results in hospital practice depend on good teamwork between several specialists. In a number of patients with urinary tract infections a remediable obstruction will be discovered. When corrective measures have been undertaken and the proper antimicrobial therapy has been given, a permanent cure can be achieved in a substantial percentage of those cases. The majority, however, has an established chronic pyelonephritis, where a bacterial cure probably does not occur in more than 10% in spite of all efforts (8, 12, 13, 16, 21). Here the bacteriologist can do nothing but determine the best drug for an ever-changing series of microbes. — The correlation between antibiotic sensitivity and clinical results is dubious in chronic cases, but close to 90% in uncomplicated infections (12).

The natural course of urinary infections, uninfluenced by treatment, is toward healing. This process, however, may not be without sequelae. Scars of variable sizes in the renal parenchyma and vascular lesions remain. — Whether a kidney, once infected, is rendered more susceptible to subsequent infection is not known. A remarkable number of patients who recover from the initial infection have relapses later, however. Frequently the relapse has been caused by microbes of the same species, that caused the initial infection. It has been suggested, that this implies that the organism persists somewhere in the urinary tract, but does not appear in the urine in the free interval between acute episodes (5). — In chronic cases the kidney exhibits micro-obstructive scars within the nephron causing an intraparenchymal hydronephrosis as well as the more obvious changes in the calyces and pelvis. When an exacerbation has been "cured", the scars still remain, creating stagnant micro-pools, where bacteria are easily trapped, multiply and cause new flare-ups.

Apart from the possibility of a complicating structural abnormality, two further factors in the management of urinary infections are of importance: the dosage of the drug and the duration of therapy. Since initial infections are usually due to microbes susceptible to one or more drugs, while relapses often are caused by highly resistant species, the first round of treatment may be of special importance.

Most antimicrobial drugs are excreted through the glomeruli and concentrated in the tubuli. Small doses, so-called "urinary doses", are sufficiently concentrated to sterilize the urine promptly, but the under-

lying infection in the renal parenchyma is only masked by insufficient concentrations of the drug (11). — The consensus is now that the drug selected should be given in full systemic doses.

The majority of drugs available for treatment of urinary infections are principally bacteriostatic in their action and depend on host mechanisms for the final eradication of bacteria. While bactericidal activity would be preferable to abolish foci of infection in the parenchyma, which may be the source of persisting or recurrent infections, drugs exerting such an effect are potentially toxic like polymyxin and neomycin. At present prolonged medication with whatever drug is active against the causative microbes seems to be the only solution.

In acute infections an energetic treatment with full doses of the proper antibiotic for at least 10–14 days is often accepted as the safest method (4). In relapsing cases the habit of looking at urinary infections as a series of brief, unconnected episodes, is to accept discontinuity in therapeutic management of a disease that is continually active. Where irreversible anatomic changes prevent a permanent cure, a plea for long-term treatment has been advocated by an increasing number of authors (7, 15, 20, 21, 23, 24, 25). It is presumed that each repeated attack causes further damage to the kidneys. By long-term medication they hope to retard the progressive destruction of renal parenchyma and give symptomatic relief.

In Table 2 we have condensed methods of various workers for management of both acute and recurrent infections. The wide variations practiced are obvious, cf.

Campbell's method in acute cases with that of McCrory & Macaulay. Nevertheless the definite trend to a longer duration of antibacterial therapy is striking. As yet there is no generally accepted schedule of long-term management, but irrespective of the type of drugs, they are either given continually or in short, repeated intervals.

The selection of drugs should preferably be based on bacteriological identification and sensitivity determinations to have an optimal effect against an ever-changing flora.

A long-term medication should be tailored to suppress the infection. Too large a dose may result in a transient elimination of bacteria, but reinfection with drug-resistant bacteria occurs frequently (12). The "maintenance" dosage consequently should be small. About $\frac{1}{2}$ – $\frac{1}{4}$ of a full dose, divided into 4 equal parts, spaced to maintain a low, continuous concentration in the urine, seems to be a fairly common usage.

Summary

The evaluation of "positive" urine cultures is discussed with special reference to urine as an excellent culture medium, where rapid multiplication of microbes is possible. The importance of time and temperature on the interpretation of a bacterial culture is stressed. In dubious cases quantitative cultures may help to differentiate between contamination and true bacteriuria. Admitting the necessity of diagnostic catheterization, the danger of iatrogenic urinary infections is mentioned. — Realizing the necessity of treating urinary infections in general practice

TABLE 2.

Author	Type of infection	Drug	Dosage	Duration of treatment			Material
				Initial	Long-term		
					Continuous	Periodical	
Campell	acute	Sulfonamides or anti-biotics	full	6-7 days		children	
Engel	acute recurrent	Sulfonamides &/or antibiotics	full > reduced	7 days	4-6 months	children	
Lippman	recurrent	Nitrofurantoin	full > reduced		1-2-3-years	children & adults	
Mc Crory & Macaulay	acute	Sulfonamides	full > reduced	10 days	> several weeks	children	
Rieser	acute	Sulfonamides & tetracycline	full	2-3 weeks			
	recurrent	a sulfonamides & tetracycline	full	3 weeks		children & adults	
	active chronic	b sulfonamides tetracycline &/or sulfonamides	reduced reduced		3-5 weeks months years		
Stansfeld	recurrent	Sulfonamides & anti-biotics	full reduced	10 days	several months	children	
Rhoads	recurrent	Sulfonamides & anti-biotics					
Taylor	recurrent	(1) Broad spectrum antibiotics b sulfonamides	a) full b) reduced	5-7 days	6 weeks	1 week/2-3 weeks adults	
		(2) = la & b	a) full b) reduced	5-7 days		adults	
Weyrauch	recurrent active chronic	Sulfonamides or anti-biotics	reduced c) full b) reduced	4-6 weeks	month years month years	2 weeks/1 month children & adults	

without bacteriological findings, the importance of precise identification and determination of antimicrobial sensitivity in recurrent infections is emphasized. The

increasing tendency of treating urinary infections as a continuous process with long-term management of antibiotics is referred to.

Infections des voies urinaires. I. Médicaments et microbes dans les infections de voies urinaires du point de vue bactériologique

L'évaluation des cultures d'urine « positives » est discutée avec une référence particulière au fait que l'urine est un excellent moyen de culture où on peut obtenir une rapide multiplication des microbes. On insiste sur l'importance du temps et de la température pour l'interprétation d'une culture de bactéries. Dans des cas douteux, des cultures quantitatives peuvent aider à différencier une contamination d'une vraie bactériurie. En admettant la nécessité d'un cathétérisme de diagnostic on mentionne le danger d'infections urinaires iatrogéniques. Tout en réalisant la nécessité de traiter les infections urinaires en médecine générale sans découvertes bactériologiques, on attire l'attention sur la grande importance d'une identification précise et d'une détermination de la sensibilité anti-microbienne dans les infections périodiques. On fait allusion à la tendance de plus en plus grande à traiter les infections urinaires comme un processus continu avec une médication d'antibiotiques de longue durée.

Infektionen des Harntrakts. I. Drogen und Bakterien bei Harntraktusinfektionen vom bakteriologischen Gesichtspunkt aus gesehen

Es wird die Auswertung von „positiven“ Urinkulturen mit besonderer Berücksichtigung des Urins als ausgezeichnetem Nährboden, auf dem eine schnelle Vermehrung der Mikroben möglich ist, diskutiert. Es wird die Bedeutung von Zeit und Temperatur bei der Bewertung von Bakterienkulturen unterstrichen. In zweifelhaften Fällen können quantitative Kulturen helfen, zwischen einer Kontamination und einer echten

Bakteriurie zu unterscheiden. Es wird die Notwendigkeit der diagnostischen Katheterisierung anerkannt, jedoch die Gefahr iatrogener Harntraktinfektionen erwähnt. In Anerkennung der Notwendigkeit, Harntraktinfektionen in der allgemeinen Praxis ohne bakteriologische Befunde zu behandeln, wird die Wichtigkeit einer genauen Identifizierung und Bestimmung der antimikrobiellen Empfindlichkeit bei Rückfallinfektionen betont. Es wird außerdem Bezug genommen auf die zunehmende Neigung, Harninfektionen als einen andauernden Prozeß durch Verabreichung von Antibiotika auf lange Frist zu behandeln.

Infecciones del aparato urinario. I. Drogas y bacterias en las infecciones del aparato urinario desde el punto de vista bacteriológico

Se discute la evaluación de cultivos «positivos» de orina con referencia especial a la orina como un excelente sustrato de cultivo, donde es posible una rápida multiplicación de microbios. Se subraya la importancia del tiempo y de la temperatura en la interpretación de un cultivo bacteriano. En casos dudosos, los cultivos cuantitativos pueden ayudar a distinguir la mera contaminación de la bacteriuria auténtica. Admitiendo la necesidad del cateterismo diagnóstico, se menciona el peligro de infecciones urinarias iatrogénicas. Aceptando la premisa de tratar las infecciones urinarias en la práctica general sin hallazgos bacteriológicos, se subraya la importancia de una identificación precisa y determinación de la sensibilidad antimicrobiana en las infecciones recurrentes. Se menciona también la tendencia creciente a tratar las infecciones urinarias como un proceso continuo, con administración de antibióticos a largo plazo.

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II. Urologic Viewpoints on the Treatment of Urinary Tract Infections in Children

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Much attention has been concentrated on chronic infections of the urinary tract. However, this is no reason for disregarding the so-called "simple" cystitis, which often paves the way for chronic and hard-to-cure infections.

It has earlier been stated by several investigators that about 50 per cent of patients suffering from chronic urinary tract infections have anomalies in the urinary passages that predispose to infection (7). These anomalies may be of many

different kinds, ranging from hydronephrosis to urethral obstructions. They all have in common an impaired urinary outflow accompanied by residual urine in the renal pelvis, ureters or urinary bladder. We are well acquainted with at least some of these anomalies that can be clinically diagnosed and generally treated by surgery. Though a slight overstatement, it may be claimed that, from a clinical point of view, only a few details remain to be elucidated in this group. This applies especially to the so-called *bladder neck obstructions* and to the *urethral valves*.

Granted that half of the patients with chronic infections can be shown to have anomalies, the question remains why the other half are subjected to prolonged infection.

It may be asked whether there are any methods of investigating these patients more closely to detect reasons for the chronicity of their infections. When studying this problem, there are two conditions that have not earlier been sufficiently considered, or have been relatively unknown. They are the vesico-ureteral reflux and the renal dysplasia.

Vesico-ureteral reflux refers to the retrograde spurting of urine from the bladder into the ureters and renal pelvis at each micturition and sometimes also between micturitions. In a material comprising about 300 children with non-obstructive urinary tract infections, reflux occurred in 35% (22). It was bilateral in half of the cases and equally common among boys and girls. In half of the reflux cases dilatation of the upper urinary passages was found. Recent investigations of a large number of normal children have shown that reflux does not occur in normal

children (21, 22). This finding agrees with the majority of studies on this problem.

The normal protective mechanism against reflux is a matter of debate. Merely an increase in bladder pressure is not enough to produce reflux. Nor has the width of the ureteral orifice the significance generally attributed to it, for reflux has been ascertained even when inspection has revealed a normal orifice (4, 16, 22, 25, 27). Reflux is commonly believed to be prevented by compression of the ureter against the bladder wall. The oblique course of the ureter through the bladder wall and the length of its intramural segment have therefore been considered of the utmost significance (16, 17). A weakening of the bladder wall, in certain cases due to diverticulum formation, has been believed to involve a loss of support to the ureter which would be the principle cause of the reflux (20). Reflux can be produced by experimental edema formation in the bladder wall around the ureter (2). Thus suspicion is raised of the possible significance of the first acute bladder infection as a reflux-producing factor.

In many cases reflux undoubtedly occurs as the result of an acute infection which produces a disturbance in the normal closing mechanism at the passing of the ureters through the bladder wall, and not due to a change in the ureteral orifices themselves.

Reflux more easily occurs in children than in adults (22). By early and adequate treatment of the urinary tract infection the reflux may disappear (22). Spontaneous regression is not unlikely.

If the reflux becomes permanent, the upper urinary passages are exposed at each micturition to a transmission of the blad-

der pressure. This entails a risk of failing function of the ureter and dilatation of the upper urinary tract as well as danger of repeated infections. Thus, a true vicious cycle would be manifest: infection causes reflux, which in turn leads to repeated infections.

Other possibilities of an ascending spreading of the infection via the ureteral lumen, owing to a stagnating column of fluid, or continuously via the ureteral wall lymphatics cannot be definitely excluded.

Renal dysplasia is a congenital malformation of the renal parenchyma. Earlier much was written about the so-called renal hypoplasia. The latter term has increasingly come to denote small kidneys, irrespective of whether they are the outcome of a congenital malformation or of a secondary post-infectious atrophy. The main interest in the literature has therefore been focussed on these miniature kidneys. The prerequisite for normal kidney development is considered to be a contact between the ureteral anlage from the Wolffian duct and the metanephrogenic blastema (5, 15, 19). If this contact fails to occur, the induction which causes the blastema to develop into renal tissue is absent. The result is renal aplasia or such a marked dysplasia as to bring forth a kidney that is only a small tissue fragment, lacking all functional ability. If only one or a few of the branches of the ureteral anlage lack a normal contact with the blastema, the defective development will be limited to a very small part of the kidney.

Several investigators have claimed that renal dysplasia cannot be distinguished from atrophy, whether clinically, radiologically or microscopically, as the conge-

nital changes are masked by secondary, postinflammatory changes (9, 26). Some claim it possible to diagnose dysplasia, either radiologically (10) or by microscopic examination of the renal parenchyma (11-13, 23-24). In certain cases the dysplastic area is too small to be detected by radiologic methods and only microscopic examination of renal tissue can definitely determine the presence of dysplasia. Puncture biopsy, which is useful in more generalized renal processes will probably not be useful in these cases with such small dysplastic areas.

Dysplasia is commonly considered to predispose to infection (7, 9, 10, 11-13, 14, 18, 23-24). It has also been stated to predispose to arterial hypertension (1, 6, 18, 23). It still remains to be established how dysplasia renders a patient more susceptible to infection. Analyses of experimental pyelonephritis show that infection occurs primarily, or exclusively, in renal scars, whether they have been caused by an earlier healed pyelonephritis or by electro-cautery. This is evident whether the bacteria are introduced by intravenous injection or by application into the urinary bladder (3, 8). In a series of 34 children, with recurrent infections, in whom part of the renal parenchyma could be microscopically examined, 31 had dysplasia (11-13). The dysplasia was particularly common in cases with duplication of the upper urinary tract. The clinical significance of such duplications has received much previous discussion. This malformation is considered by many as unimportant; others again believe that it predisposes to infection. The latter statement has proved hard to explain.

The high incidence of dysplasia is perhaps an explanation.

In discussing the practical, clinical management of patients with urinary tract infections, the three following questions seem important to answer:

1. *In which cases is a more thorough examination of the urinary tract indicated?*

Such examination should be undertaken in all cases that have been subjected to three infections within a short time despite apparently adequate medical therapy. Infants constitute a clinical group of their own. The younger a patient is when falling victim to infection, the greater the probability of existence of congenital anomaly. Consequently, the younger the patient with infection, the greater the indication for thorough urological investigation. Early diagnosis and treatment are the best hope for healing before serious irreversible renal injury has developed. Furthermore, it should be borne in mind that urinary tract infections in infants sometimes are manifested by generalized, non-specific symptoms that are not directly indicative of the site of infection. In most instances all the different types of obstruction lack pathognomonic symptoms. That applies even to the urethral valves which, from a theoretical point of view, could give rise to micturitional difficulties. Refluxes and dysplasias are entirely lacking in typical clinical symptoms and can only be detected by complete examination.

2. *Which examinations are to be performed, and what in particular is to be looked out for?*

As well as the complete urine analysis with bacteriologic cultures and antibiotic

resistance determinations, the examination should comprise *intra-venous urography*, *micturition urethrocystography* and *endoscopy*. Obstructions of any kind should be detected, but will not be discussed in this paper. An estimation of the urethral and ureteral changes, in particular, may be difficult. The reflux can only be diagnosed by means of urethrocystography (Fig. 1). A dysplasia can be diagnosed when it produces an abnormally small kidney or a conspicuous local reduction of the renal parenchyma as demonstrated by the urographic film. The lesser degrees of dysplasia, which are equally liable to infection, cannot be diagnosed by the usual, clinical methods.

3. *How are infections to be treated to prevent recurrence or chronicity?*

Owing to the risk of reflux after a so-called "simple" cystitis, such infection in a child should be regarded as a disease calling for careful therapeutics and observation. By means of early and adequate treatment the reflux may be prevented or cured. When treating an acute urinary infection, only chemotherapeutic agents such as sulfa drugs, furadantin, or the like, should be employed initially. Antibiotics should be withheld until a more detailed urological investigation and bacterial analysis has been made. The dosage should be kept high. Previous recommendations to use lower dosages in urinary tract infections than in other infections do not seem to have been well-founded. In cases with normal renal function the urine is strongly concentrated during its passage from the glomeruli to the renal pelvis and, accordingly, also the drug. But a urinary tract



Fig. 1. Girl, 3 months old. Recurrent cystopyelitis. No true obstruction. Intravenous urography normal, no dilatation of the upper urinary tract. At micturition urethrocytography marked reflux to both ureters and pelvis which dilate considerably during micturition. Vagina, too, is outlined which is a normal finding.

infection must not be considered an infection only in the urine. The infectious foci are to be found in the renal parenchyma, in the ureteral and bladder walls, and are not affected by a high concentration of the drug in the urine. Therapeutic agents will reach those foci mainly via the blood and interstitial fluid. The blood concen-

tration of the agent is of more decisive significance than its urine concentration. Moreover, in renal infection the concentration capacity is often reduced.

Summary

The surgical treatment should, as far as possible, remove any anomaly and provide

the most favourable conditions for continued medical treatment. All obstructions should be relieved. The reflux can in certain cases be treated by surgery, but the final success of surgical treatment remains to be fully elucidated. The selection of cases for surgery should be made with some care until the results of surgical treatment is better evaluated. Dysplasia also can be treated by surgery, on condi-

tion that the changes can be located and are restricted to only one kidney, or part of the renal parenchyma which can be resected. In the most subtle cases, suspected only from long experience, conservative treatment and observation will have to suffice for the time being, and prolonged medication will no doubt be extremely important.

Infection des voies urinaires. II. Point de vue urologique dans la traitement des infections des voies urinaires chez les enfants

Le traitement chirurgical devrait autant que possible faire disparaître toute anomalie et fournir les meilleures conditions pour un traitement médical continu. Toutes les obstructions devraient être enlevées. Le reflux peut en certains cas être traité par la chirurgie, mais le succès définitif du traitement chirurgical reste à élucider. La sélection des cas de chirurgie devrait être faite avec soin en attendant de pouvoir mieux évaluer les résultats des interventions chirurgicales. La dysplasie peut également être traitée par la chirurgie, à condition que les changements puissent être localisés et limités à un seul rein ou à une partie de la parenchyme pouvant être réséquée. Dans les cas les plus difficiles, reconnaissables seulement grâce à une longue expérience, un traitement conservateur et l'observation devront suffire, et une médication prolongée sera sans doute d'une grande importance.

Infektionen des Harntrakts. II. Urologische Gesichtspunkte über die Behandlung von Harntraktusinfektionen bei Kindern

Die chirurgische Behandlung sollte so weit wie möglich alle Anomalien beseitigen und günstigste Bedingungen für eine fortdauernde ärztliche Behandlung schaffen. Alle Obstruktionen müssen entfernt werden. Der Rückfluß kann in gewissen Fällen chirurgisch behandelt werden, der endgültige Erfolg einer chirurgischen Behandlung ist jedoch noch nicht vollkommen klar. Die Auswahl von Fällen für eine chirurgische Behandlung muß sorgfältig vorgenommen werden, bis die bisher erzielten Ergebnisse der chirurgi-

schen Behandlung besser ausgewertet sind. Die Dysplasie kann ebenfalls chirurgisch behandelt werden, jedoch unter der Bedingung, daß die Veränderungen lokalisiert werden können und sich auf eine einzige Niere beschränken, oder auf ein Teil des Nierenparenchyms, das reseziert werden kann. In subtileren Fällen, die nur auf Grund langer Erfahrung vermutet werden, muß die konservative Behandlung und Beobachtung vorerst noch ausreichen, und die langandauernde Medikation ist ohne Zweifel äußerst wichtig.

Infecciones del aparato urinario. II. Puntos de vista urológicos sobre el tratamiento de infecciones del aparato urinario en los niños

El tratamiento cirúrgico debía, en lo posible, hacer desaparecer todas las anomalías y crear las condiciones más favorables para un tratamiento médico continuo. Deben eliminarse todas las obstrucciones. El reflujo puede, en ciertos casos, ser tratado por cirugía, pero el éxito final de este tratamiento queda aún por elucidar del todo. La selección de casos por someter a cirugía tiene que realizarse con cierto cuidado, hasta que se hayan evaluado mejor los resultados del tratamiento cirúrgico. También la displasia puede ser tratada por medios cirúrgicos, con la condición de que las modificaciones puedan ser localizadas y que se limiten a uno solo de los riñones o a una parte del parénquima renal que podría ser extirpada. En los casos más sutiles, sospechados únicamente a raíz de largas experiencias, el tratamiento conservador y la observación deberán ser suficientes por ahora, siendo, sin duda, la medicación prolongada de extrema importancia.

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III. Acute Pyelonephritis in Childhood: Evaluation of Criteria of Successful Medical Treatment¹

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An acute, febrile urinary tract infection during infancy or childhood affects—even in its clinically mild form—often the renal parenchyma, causing an impairment of renal function which is similar to that observed in chronic pyelonephritis (7, 11). Although comprehensive reports on the fate of infants and children with such infections are lacking, there are some observations to suggest that the long-term prognosis may be more serious than an initial disappearance of clinical signs and symptoms would suggest (1, 6, 8, 10, 12).

Therefore it seems especially important to diagnose and treat the acute pyelonephritis adequately and to check the results of the treatment. Because of the special difficulties in obtaining "sterile collected" urine specimens in infants and small children the check up in pediatric practice often does not include a urine culture; instead the result of the treatment is evaluated on the basis of such indirect evidence of cure as disappearance of clinical symptoms of infection, normalization of the urinary sediment and the erythrocyte sedimentation rate. The purpose of the present investigation was mainly to evaluate critically whether these evidences are useful as proof of successful treatment.

Material and Methods

Material

The present communication is based upon a study of 38 infants and children who had had one or more acute nonobstructive urinary tract infections. From this original material were selected 28 patients who on a check up 4–7 weeks after disappearance of fever had a normal urinary sediment and were free from clinical symptoms of infection. Five patients, all female, were omitted from the study because a pyuria indicated the presence of infection at the check-up 4–7 weeks following the disappearance of fever. Another five because urine cultures had been performed at such great intervals that the duration of bacteriuria could not be established with any degree of certainty.

In the 28 patients selected for the study, urine cultures and in vitro sensitivity tests were performed two or three times during the first three weeks following the onset of infection. Later check-ups were performed at least once during the 4th–7th week following disappearance of fever and after this time once a month until two or three consecutive, negative specimens were obtained.

Eighteen of the selected patients were females, ten were males; 14 were below the age of one year. Intravenous urography was performed in all patients; duplication of the upper urinary tract was present in four. No other anatomical malformations were seen. Micturition urethro-cystography was performed in 26 patients. There was no obstruction of the urinary stream. Vesico-ureteral reflux was demonstrated in 10 patients. The initial causative microbe was

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E. coli in 23 cases, proteus in three, aerobacter aerogenes in one and unknown in one case.

Laboratory Methods

In the male patients voided urine specimens—obtained after thorough cleaning of the penile foreskin, glans and meatus—were generally used for culture and sediment investigation. In patients with prolonged bacteriuria the result was checked by culture of urine specimens obtained by catheterization. In the female patients urine was usually obtained by catheterization of the bladder during the first weeks following infection. Later on voided specimens were sometimes sent for investigation, because of the risks for reinfection inherent in bladder catheterization (1, 4, 5). In these instances a culture was never judged as positive until the result had been confirmed by culture of a specimen obtained by catheterization. The urine specimens were transferred to the bacteriological laboratory within one or two hours after they were obtained.

TABLE 1. *Principles of chemotherapy in the investigated material.*

Number of days	Gantrisin (sulfisoxazole) dose in mg/kg bw/24 hours
10	200 (-150)
21	100
28 or longer	25-50

TABLE 2. *Urine culture, urinary sediment, ESR and vesicoureteral reflux in 28 infants and children 4-7 weeks after an acute, nonobstructive urinary tract infection. All patients lacked symptoms of disease at the time of investigation.*

	Number of cases					Vesico-urteral reflux
	Males	Females	Urinary sedi- ment negative	ESR > 20 mm/hour	ESR < 20 mm/hour	
Urine culture positive (14 patients)	9	5	14	0	12	4
Urine culture negative (14 patients)	1	13	14	1	13	6

Chemotherapeutic Treatment

The patients were treated in accordance with the schedule given in Table 1. When bacteria resistant to sulfa were cultured an adequate antibiotic, as judged by *in vitro* sensitivity test, was given in systemic doses for 7-10 days, and then followed by gantrisin in reduced doses according to the schedule.

Results

Table 2 shows that when investigated 4-7 weeks after the disappearance of fever 14 of the 28 patients had a positive urine culture in the presence of a normal urinary sediment. All patients looked healthy and lacked clinical symptoms of persisting infection. The ESR was below 20 mm/hour in all patients with positive culture. In five of the 14 patients with persisting bacteriuria the renal concentration capacity was investigated during the acute stage of the infection and at the check-up 4-7 weeks later. In all the concentration capacity was lowered during the acute stage but within normal limits at the check-up (cf. 11).

The bacteria cultured at the check-up had all to be looked upon as pathogens (Table 3). In addition to the bacteria listed enterococci were cultured in several instances.

The duration of the bacteriuria was very long in several of the male patients

TABLE 3. *Urine culture 4-7 weeks after an acute pyelonephritis in 14 patients with negative urinary sediment.*

Type of bacteria	Number of cases
<i>E. coli</i>	8
<i>Proteus vulgaris</i>	4
<i>Pseudomonas aeruginosa</i>	1
Several microorganisms	1

(Table 4). In all patients except one, the bacteriuria eventually disappeared as judged by two or three consecutive, negative cultures. In the female patients the duration of the bacteriuria was in all cases less than 2 months.

TABLE 4. *Duration of the bacteriuria after an acute, nonobstructive urinary tract infection. The series consists of 10 boys.*

Duration of bacteriuria in months	Number of cases	Duplication of the upper urinary tract	Vesico-ureteral reflux
9	1	0	0
7	1	0	0
2-4	3	0	2
1-5	4	2	0
<1	1	1	0

In this small series there was no correlation between the duration of the bacteriuria and the presence of vesico-ureteral reflux (Table 2).

Among the five patients omitted from the study because of an insufficient number of check-ups, three had normal sediment and were free from symptoms in spite of persisting bacteriuria when a check-up was performed.

Among the five patients excluded because of positive sediment at the check-up 4-7 weeks following subsidence of fever

one had a low 24 hour endogenous creatinine clearance one year after the last infection, one had an impaired concentration capacity more than one year after the last acute infection, two have had persistent symptoms of infection during the following 12-18 months and one is untraced. These patients had all—except the untraced one—vesico-ureteral reflux.

Comment

The investigations show that after non-obstructive, adequately treated, acute urinary tract infections in infancy and childhood a bacteriuria may persist for a long time. It is also evident that a negative urinary sediment, a normal ESR and the absence of clinical symptoms of infection form a very unreliable base in estimating the result of treatment as regards eradication of infection. The findings are in accordance with those of Jackson, Griebble & Knudsen (2) investigating adults with anatomically proven chronic pyelonephritis. These authors found pyuria to be absent in 22 per cent of the cases. Kass (4, 5) has also arrived at conclusion that in cases with suspected pyelonephritis the urinary sediment, when negative, and the absence of clinical symptoms are of little value diagnostically.

The import and origin of the persisting bacteriuria is not evident. The bacteriological methods employed in this study have tent to reduce—although not exclude—the possibility of "contamination bacteriuria". The high incidence of pathogenic bacteria—which is not typical of "contamination bacteriuria" (cf. 1)—and the constancy of the bacteriological findings when repeated cultures were performed,

suggest that in most instances the bacteriuria was a "true" one. In addition most positive cultures were obtained when chemotherapy was going on. In adults such bacteriuria, especially when following acute infections of the urinary tract, is often associated with active infection of the renal parenchyma as shown by MacDonald, Levitin, Mallory & Kass (9) and by Jackson, Poirier & Griebel (3).

Thus, available information does not speak against the possibility that the bacteriuria demonstrated may be due to a persisting infection of the renal parenchyma and consequently require antibacterial treatment. An acute urinary tract infection can therefore not be considered to be adequately treated until persistence of bacteriuria is excluded by proper methods of urine culture. Preferably repeated cultures should be performed since excretion of bacteria may be intermittent.

It was mentioned in the introduction that there were investigations to suggest that the long term prognosis of acute pyelonephritis appearing in childhood might be serious. It does not seem improbable that this dubious prognosis may have some relation to the asymptomatic bacteriuria which may follow the acute pyelonephritis in some instances.

Summary

Thirtythree infants and children with acute, nonobstructive pyelonephritis were treated and checked after treatment according to a fixed scheme.

In five patients persisting pyuria 4-7 weeks after disappearance of fever indicated persisting infection at that time.

In 28 patients there was a normal urinary sediment, a normal erythrocyte sedimentation rate and absence of all clinical symptoms of infection at a check-up 4-7 weeks after the disappearance of fever. Among these 28 patients no less than 14 were found to have a positive urine culture.

It is concluded that the urinary sediment, the erythrocyte sedimentation rate and the absence of clinical symptoms are of limited value in evaluating even the immediate result of the treatment.

The import and origin of the bacteriuria is discussed. It might be due to an active infection of the renal parenchyma and thus require intensive antibacterial treatment. It is therefore stressed that the proper treatment of acute pyelonephritis necessitates repeated urine cultures during the weeks or months following disappearance of symptoms.

The interrelation between such asymptomatic bacteriuria following an acute infection and the dubious long-term prognosis of acute pyelonephritis is discussed.

Infections des voies urinaires. III. Pyélonéphrite aiguë. Evaluation des critères de traitements médicaux qui réussissent

Trente-trois nourissons et enfants atteints de pyélonéphrite aiguë non obstructive furent traités et contrôlés après traitement suivant un plan fixe. On conclut que les sédiments urinaires, le taux de sédimentation érythrocyte et l'absence

de symptômes cliniques sont de valeur limitée pour l'évaluation du résultat immédiat du traitement. L'importance et l'origine de la présence de bactéries dans l'urine est discutée. Elle peut être due à une infection active de la parenchyme rénale et donc nécessite un traitement antibactérien intensif. C'est pourquoi il est nécessaire pour bien traiter une pyélonéphrite aiguë

de faire des cultures répétées d'urine pendant les semaines et les mois qui suivent la disparition des symptômes. La relation entre une telle bactériurie asymptomatique suivant une infection aiguë et la prognose douteuse à long terme d'une pyélonéphrite aiguë est discutée.

Infektionen des Harntrakts. III. Akute Pyelonephritis. Bewertung von Kriterien betreffs einer erfolgreichen ärztlichen Behandlung

33 Kleinkinder und Kinder mit akuter, nicht obstruktiver Pyelonephritis wurden behandelt und nach der Behandlung gemäß einem festen Schema untersucht. Es wird aus den Ergebnissen geschlossen, daß das Urinsediment, die Erythrozytensenkungsgeschwindigkeit und die Abwesenheit von klinischen Symptomen nur von begrenztem Wert sind, auch wenn es sich um die Auswertung der unmittelbaren Ergebnisse einer Behandlung handelt. Es wird die Bedeutung und der Ursprung der Bakteriurie diskutiert. Sie kann auf einer aktiven Infektion des Nierenparenchyms beruhen und so eine intensive antibakterielle Behandlung erfordern. Es wird daher betont, daß die eigentliche Behandlung der akuten Pyelonephritis wiederholte Urinkulturen während der Wochen und Monate nach dem Verschwinden der Symptome verlangt. Es

werden die Wechselbeziehungen zwischen solch einer asymptomatischen Bakteriurie als Folge einer akuten Infektion und der zweifelhaften Prognose auf lange Sicht der akuten Pyelonephritis diskutiert.

Infecciones del aparato urinario. III. Pielonefritis aguda. Evaluación de criterios sobre el tratamiento médico con resultado positivo

33 infantes y niños con pielonefritis aguda no obstructiva fueron tratados y explorados después del tratamiento conforme a un esquema prefijado. Se concluye que el sedimento urinario, la velocidad de la sedimentación eritrocítica y la ausencia de síntomas clínicos son de valor limitado al evaluar incluso el resultado inmediato del tratamiento. Se discute la importancia y el origen de la bacteriuria que puede deberse a una infección activa del parénquima renal y, por lo tanto, requerir un tratamiento antibacteriano intensivo. Por ello se subraya que el tratamiento propio de la pielonefritis aguda necesita repetidos cultivos en orina durante las semanas y los meses siguientes a la desaparición de los síntomas. Se discuten las relaciones entre tal bacteriuria asintomática siguiendo a una infección aguda y el dudoso pronóstico a largo plazo de la pielonefritis.

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SUMMARY OF SUPPLEMENT

Idiopathic Chronic Megaloblastic Anemia in Children.

by OLGA IMERSLUND

Supplement 119

On the basis of a study of 10 patients from 6 different families living in South-Eastern Norway a chronic relapsing familial occurring megaloblastic anemia in children has been described. This disease entity has not previously been separated as such. Males and females have been affected, and only siblings, not parents. No consanguinity has been demonstrated between parents, of whom 3 couples come from relatively isolated valleys.

The onset of symptoms was from 5–6 months to 4 years of age. The symptoms and signs at onset and during relapse have been pallor, weakness, irritability, dyspnoea, fever without apparent cause, gastrointestinal disturbances, loss of appetite, vomiting, glossitis, tendency to diarrhoea or constipation, slight jaundice, and systolic murmurs over the heart. Slight or doubtful transient neurological changes have been observed in 3, hemorrhagic manifestations not always related to thrombopenia in 7, and edema in 10. Premature greying of the hair was already observed in one case at the age of 11. Growth and development have been within the normal range, as has intelligence. The anemia has been normochromic or slightly

hyperchromic with a tendency to moderate leucopenia, an increased serum color, serum iron, erythrocyte sedimentation rate, and with low plasma vitamin B₁₂ values. The Price Jones curves and findings in the bone marrow were indistinguishable from those in pernicious anemia. Eight of the 10 patients have permanent proteinuria, with familial occurrence and without signs of impaired renal function, as judged by the specific gravity of the urine and the urea and endogenous creatinine clearance tests, even in the eldest patient after 17–18 years duration of the disease. On electrophoretic examination the protein has been identical with the serum protein. Sixty-one to one hundred percent of the total urinary protein has been albumin. In 2 of the 10 patients, 2 siblings with proteinuria, hyperaminoaciduria has been demonstrated. Five of the 10 have urinary tract anomalies of a relatively homogenous appearance which may be regarded as representing different stages, from slight to complete, of duplication of the urinary pelvis and ureter. Only one of the 10 has neither proteinuria nor urinary tract anomalies.

The anemia has shown a specific re-

response to treatment with folic acid and liver perorally, injections of liver extract, and vitamin B₁₂. On discontinuation of the specific antipernicious treatment clinical remissions lasting up to 14-15 months have occurred. Spontaneous remissions have not been observed. Such known causes of megaloblastic anemia as celiac disease, gross pathological changes in the gastrointestinal tract including tumors, stenoses, adhesions, anastomoses, massive diverticulosis and regional ileitis, as well as cirrhosis of the liver, deficient nutrition, infections and intoxications have been ruled out.

The anemia differs from pernicious anemia in the following respects: lack of gastric achlorhydria, even after an Ewald's test meal; presence of normal volume and acidity of the gastric juice when examined after injection of histamine; findings suggesting normal intrinsic factor activity, i.e. lack of effect of perorally administered vitamin B₁₂ + pooled normal gastric

juice, and normal quantities of microbiologically determined vitamin B₁₂ binding factor in the gastric juice.

The data suggest that an intestinal malabsorption of vitamin B₁₂ or a metabolic defect or a combination of these factors is of pathogenetic importance. The underlying defect (or defects) is probably congenital or becomes manifest after a period of latency and is inherited as a recessive trait linked with a tendency to proteinuria, and possibly also urinary tract anomalies.

No case of adult pernicious anemia was found among the patients' relatives.

Out of 60 deaths assigned to known disease among the patients' relatives (parents, aunts, uncles, cousins, grandparents and grandparents' siblings) 6.7 percent were caused by gastric cancer, a figure which does not seem to suggest a greater incidence of this disease among the relatives than in the total population.

PROCEEDINGS OF PEDIATRIC SOCIETIES

Swedish Pediatric Society

Meeting September 12, 1959

Gösta Nordenhem: A case of suspicious cortico-adrenal insufficiency

A 6-year-old girl whose mother died in 1954 with the diagnosis of left renal malignant neoplasm with pulmonary metastases. Patient's previous history mostly normal. Patient has had since 1956 angular stomatitis and white coating of the tongue. Since 6 months of age she has had vigorous attacks of constipation, without defecation up till 4-5 days. Feces has been hard and ball-shaped. Since 1959 she has been very feeble and tired at times and has suffered abdominal pains. Since July 1959 she has preferred salty food as for example pickled herring. On Aug. 17 she experienced abdominal pains and was listless. Physician attending her the following day removed hard masses of scybalum-balls. Her last defecation was on Aug. 13. When she began vomiting she was admitted to the Children's Clinic on Aug. 19. Her general condition was malaised, with reduced turgor and sunken eyes. Blood pressure 80/55. Colour of skin pale and slightly dirty-gray. Perianal pigmentation, but not elsewhere. Subsequently light pigmentation developed in skin areas from which adhesive tape had been removed. Liquide are injected intravenously on several occasions. Vomiting persist once or twice daily, usually some time after meals and without pain. Undigested food is regurgitated several hours after meal-time. Appetite is poor, and patient lost a good kilo in weight during the first two weeks. She is fatigued and remains in bed most of the day.

Ventricular retention is demonstrated. Test meal shows almost no free HCl. Cultures

of gastric fluid and of feces show fungi, probably monilia. X-ray of colon, lungs, esophagus and stomach show no pathological lesions. ECG is normal. Thorn's test gives no lead. Kepler's water test cannot be carried out on account of vomitings. Laboratory findings: Hb. 76 %, RBC 5.1 million, WBC 8900, hematocrit 40 vol. %. Differential count normal. Ca. 10.1 mg %, P 4.5 mg %, Na 114-120 mEq, K 4.5 mEq, Cl 76-84 mEq, CO₂-capacity 18 mEq, RN 38 mg %, serum albumin 5.84 %, fractions appear normal. Fasting blood sugar 114 mg %. Elimination of 17-ketosteroids 0.3 mg/day, 17-ketogens 1.6 mg/day.

DISCUSSION. *C. G. Bergstrand:* One cannot definitely rule out the diagnosis of Addison's disease and indications should warrant that an adrenal function test be performed. It might be preferable to administer ACTH by intravenous drip, with determination of 17-ketosteroids and 17-ketogensteroids before, during and after the use of ACTH. The normal value for 17-ketogensteroids in children's urine may not be published, but the reported value would seem rather low. — *O. Brandberg:* As a supplementary test I would recommend an EEG series before, during and after the vomiting attacks. Periodic vomiting may produce EEG changes which may suggest something about the diagnosis and above everything else about the prognosis.

Henrik Voss: Epidermolysis bullosa in families with keratosis palmaris et plantaris

Keratosis palmaris et plantaris is a disease which for more than six generations

has afflicted several families within a small mountain district in Jämtland. About 100 surviving persons with this disease are known to the investigator. As a preliminary report is presented a survey of 2 of these families with typical keratosis palmaris et plantaris. An account is given of the symptomatology of the disease and several typical cases drawn from different age-groups are demonstrated. One finds 68 persons in the one family originating in straight descending line from disease-carriers. Thirty-eight of these are in good health, and 30 have keratosis. The other family comprises 106 persons descended from disease-carriers. Fifty-three of them are in good health and 53 have keratosis. Among an equal number of persons in a family descended from healthy parents, one finds no case of the disease. Men and women transmit the disease with the same frequency and there is no significant difference between the number of affected men and women. Keratosis palmaris et plantaris is known as a typical example of simple dominant hereditary transmission of the disease. This is also confirmed by the present survey. It is especially interesting that a typical case of epidermolysis bullosa dystrophica appears in the youngest generation of each of these two families. The first case presents no known kinship between the parents. Both are in good health, but the maternal grandmother has keratosis palmaris et plantaris. Typical

papules have been present since birth in the skin and oral mucous membranes, for short periods nail-deformations appeared, and the papules healed with scar formation and pigmentation. The disposition for crops of papules has successively diminished and at 3 years of age the patient had trouble only during the summer months and the mucous membranes are completely spared. The other case presents no definite kinship between the parents, but both have keratosis palmaris et plantaris. The child was born prematurely, weighing 1760 g. Large papules were present all over the body at birth, but especially on the extremities. The child died 2 days old. In both cases the clinical diagnosis was confirmed by skin biopsy which showed lesions typical for epidermolysis bullosa dystrophica.

DISCUSSION: *H. Enell*: A family in the district of Arvidsjaur was investigated with 8 cases of epidermolysis bullosa dystrophica among 747 persons (*Acta derm.-ven.*: 34, 463, 1954). Dr. Stern Floderus at the communal hospital in this district has investigated another family there with hyperkeratosis palmaris et plantaris, but no direct connection could be established between the families and no case of hyperkeratosis occurred in the family afflicted with epidermolysis. It is probable that the appearance of 2 cases of epidermolysis in the above mentioned large families with carriers disposed to hyperkeratosis is purely coincidental.

Meeting October 9, 1959

M. Böttiger, S. Gard and R. Lagercrantz: Vaccination with live polio-virus

More than 200 million people have been vaccinated with killed polio-virus. These vaccinations represent an immense progress. New experiences among others from U.S.A. and Israel suggest that even a completed vaccination with killed polio-virus vaccine not always confers an absolute protection especially against polio-virus Type I. Experimental trials with the live attenuated polio-virus would therefore seem desirable.

Nineteen families with 41 adults and 44

children from a Stockholm Children's Welfare Center participated in a field experiment for the purpose of clarifying the virological and immunological aspects of such a vaccination. It was established that none of the 44 children had had any previous contact with live polio-virus on the basis of neutralization tests. Four of the adults were serologically "triple-negative" and further 10 lacked antibodies against polio-virus Type I. Following 2 or 3 injections with formalinized (killed) vaccine, all the experimental participants had antibodies against Type I. The

youngest child in each family then received 1 million tissue-culture units of an attenuated live polio-virus strain which was obtained from Dr. Koprowski (Type I + strain "Chat"), U.S.A. Vaccination took place during the winter months and none of the children attended day nurseries or kindergartens. All the index-children were found to eliminate virus for several weeks (average 7, maximum 12), and a spreading of the virus took place to 8 out of 25 receptive siblings, but to none of the adults, despite that 10 of these were receptive. The virus strains which were eliminated from the index-children and their siblings have been studied in detail concerning their type of growth in tissue-cultures and their pathogenicity for monkeys, without any systematic virulence enhancement of significance being found to have occurred. No manifestation of disease was observed which could be attributed to vaccination. Two months after vaccination with live polio-virus, antibodies had increased significantly in those who eliminated virus and the antibody titers had only dropped slightly and not significantly when tests were made 7-8 months later.

At this latter time the whole family was vaccinated with live attenuated polio-virus. Then it was shown that the naturally im-

mune test persons didn't eliminate any virus at all or only during a very brief period (they were "resistant"), and that those having received live virus earlier (the index-children and their infected siblings) eliminated virus on the average a little longer period, but they were also mainly resistant. On the other hand, test persons who earlier had had contact only with killed virus, they eliminated virus for a long time after vaccination. Those among the latter who had high serologic titers against Type I, they eliminated virus for a shorter period (they were more resistant) than those having lower antibody titers.

It is therefore evident that vaccination with live attenuated polio-virus confers a more complete immunity (even a local such), and in all probability a more durable serologic immunity than is produced by killed vaccine. Since our more extensive and recent field experiments have shown that the virus is spread from children under 2 years of age but not from older children, it would seem feasible that vaccination with live polio-virus should be postponed until 3 or 4 years of age. For the time being we recommend that a vaccination with killed vaccine should be carried out beforehand as a preparation for vaccination with live attenuated polio-virus.

CORRESPONDENCE

Dr. Arvid Wallgren, Chief Editor
Acta Paediatrica
Karolinska Sjukhusets Barnklinik
Stockholm 60, Sweden

Dear Doctor Wallgren:

I would like to comment upon the paper on hyperbilirubinemia by A. Mores, I. Fargašová and E. Minaříková in the November issue.

These authors found four instances of kernicterus among 31 premature infants whose peak serum bilirubin levels rose to 25 mg per cent or above, which is an incidence of 13 per cent. Nevertheless, they conclude that "we do not perform exchange transfusion in full term as well as in premature infants with high bilirubinemia if we are able to exclude that it is not caused by some isoimmunization". The reason for this conservatism is that among *all* premature infants, kernicterus is rare.

The position taken is not logical. Surely an identifiable group (those prematures with 25 mg per cent or more of bilirubinemia) whose danger of developing kernicterus is 13 per cent, deserve treatment with exchange transfusion. The mortality from the treatment itself is much less than this, as has been shown by Dr. Mary Crosse.

It is true that evidence for significant nervous damage is scarce in prematures whose bilirubin levels rise only to 15 or 25 mg per cent. Factors which intensify or which tend to decrease the neuro-toxicity of bilirubin were brought out at the International Congress of Pediatrics by Gerard Odell, by Lois Johnson, by Alfred Freedman and by Lars Ernster. Among the harmful

factors are endogenous and exogenous substances which compete for binding with albumin, low levels of serum albumin, and maleness. Protecting factors are femaleness, high levels of serum albumin and freedom from infection.

The data presented by Mores and co-workers could better be interpreted as showing the need for more research on (1) factors which modify the action of bilirubin and (2) the risk of exchange transfusion. Until a better treatment is found (and this seems possible) all premature infants with bilirubin levels of 25 mg per cent or more should be transfused. Some selection of cases is certainly rational for prematures with levels between 15 and 25 mg per cent.

As to the greater danger of bilirubinemia when intensified by hemolysis, there is some theoretical but not much statistical support. The depression of Hufner's coefficient by Rh antibody, as shown by Abrahamov, might play a role. So also might hematin, released by hemolysis. Abelson has found a hematin-like pigment in the blood in hemolytic disease; hematin is known to be toxic; hematin displaces bilirubin from albumin (Odell). These factors might play a role, but the preferred modification of treatment which they could point to would, rather, be a lowering of the bilirubin criterion for exchange from 20 mg per cent to, say, 15 mg per cent in hemolytic disease in the case of premature infants.

Sincerely yours,

Richard Day, M.D.
Professor of Pediatrics
State University of New York
College of Medicine

BOOK REVIEWS

Growth and Development of Children. E. H. Watson and G. H. Lowrey.

The Year Book Publishers, Chicago, Ill., 1958. 3rd edition. 334 pages. Price \$7.75.

The knowledge of the normal growth and development of children is the base for all pediatric activities in practice as well as in clinical work and research work. This fact has more and more been emphasized lately and the subject has been given greater attention in the pediatric teaching. However, as it includes all of the dynamic physiologic and psychologic changes taking place from conception to maturity, it constitutes a highly complex phenomenon. There is thus a great demand for an easy and clear review on this subject, which is also extensively penetrated. The 3rd edition of Watson's and Lowry's well known book is thus greatly appreciated. The material has been put up to date by changes and additions in practically all chapters, including well over a hundred new references.

After the lightening chapter on heredity and environmental factors, extensively changed, and an easy and clear, but fairly short chapter of fetal growth and development, the normal physical measurements are more thoroughly penetrated. Different American standards are given, however, several ones not in metric systems, which might be inconvenient for readers in several countries. Also somatic typing has been discussed.

The characteristics in the premature child's growth and development are given. The next chapter on behavior and personality has been extended and will stimulate even the well experienced pediatrician to reconsider the fascinating laws in a child's development.

With the anatomical growth of the main organs of the body as a background the

development of the various functions of the body is described, the physiological as well as the bio-chemical ones. The osseous development is separately described.

The chapter on the role of the endocrine glands in growth and development, largely rewritten, condenses a great deal of facts, which must give readers a valuable recapitulation of the hormonal interrelationships in the function of the body.

After discussion of the energy metabolism, the nutrition in normal growth and the dentition, the book ends, consequently, in an outline of abnormal growth.

The book gives the reader a good whole picture of that fascinating evolution which signifies the growth and the development of a child. The readers, who might like to go deeper into some aspects in this field will have good help of the reference list following each chapter.

Therefore the book can be recommended to those who work or intend to work in pediatric practice as well as to highly specialized pediatricians who like to get a general idea about the whole infant and child during the long way to maturity. Teachers of pediatrics will also have a very good use of all the condensed knowledge in the book. The authors believe that the book will be found to be useful to workers in related fields, such as those concerned with public health and elementary education, which opinion seems to be right.

Petter Karlberg, Stockholm

Le Sommeil De l'Enfant. Robert Dabré & Alice Doumic.

Presse Universitaires de France, 1959. 800 F.

Sleeping difficulties during the first three years of life are common and general practitioners and pediatricians are frequently

asked for advice. This book is a very useful source of information concerning the normal and abnormal sleep pattern in infants and children. Electroencephalography has a considerable value in the study of the physiology of sleep and well chosen EEG curves illustrate this matter. Previous studies of sleeping habits are reviewed and it is pointed out that the total duration of actual sleep in infancy is considerably less than is commonly believed. The development of the 24 hour rhythm with fluctuations between activity and sleep and the accompanying temperature variations are described. The different stages of normal sleep are dealt with and as a further introduction to sleeping problems the psychomotor and emotional development of the normal child is outlined. It is pointed out how intimately deviations from the normal in this respect are connected with sleeping difficulties. Seventy-five children with disturbed sleep observed by the authors form the basis of the discussion of these problems, and some of these are reported in detail to illustrate the different types. It is noted that each case is always different from another but that certain types are common. During the first three months of life the underlying cause is frequently a too rigid feeding schedule and the authors advocate self-demand feeding. Between 3 and 9 months of age the incidence of sleep disorders decreases but when they occur they are said to be connected with teething, a statement that seems difficult to prove. The more difficult cases occur among those 9 months to 3 years of age. Hyperactive boys with retarded speech development, emotionally disturbed children struggling for independence or subjected to physical or psychological trauma such as disease or maternal deprivation are examples from this age group. The mothers emotional stability is also of great importance. Methods of treatment are outlined including medication. The book is well written and contains a considerable amount of information in spite of its small size, including a fairly extensive bibliography.

B. Hellström, Stockholm

Urs Pulver: Spannungen und Störungen in Verhalten des Säuglings.

Verlag Hans Huber, Bern and Stuttgart, 1959. 123 pages. Price DM. 12:—.

Longitudinal studies of personality development in children are being conducted at the University of Berne under the direction of Richard Meili. In the present volume Urs Pulver gives an account of his investigations of states of tension and irritation in a group of 26 infants during their first year of life. The children have been filmed at home in various standard situations at 5 different age levels: 3, 4, 7, 9 and 11 months. The study was limited to one of "irritability" because the act of filming in itself proved to be a source of irritation for some of the infants, thus hampering the control of the experimental conditions. The author regards "irritability" as an individual variable and a personality trait observable and measurable already as early as at 4 months of age. Analysis of the film behavior at the different age levels shows that the degree of "irritability" of an infant remains roughly constant during the first year of life.

The question whether the differences in irritability among infants partly are due to differences in early maternal attitudes cannot be answered from this study according to the author. For several of the irritable infants milieu factors as well as hereditary ones could be spotted. In order to be able to encircle constitutional factors with more accuracy behind "irritability" and other early activities of infants, observations have to start earlier than at 3 months of age, preferably immediately after birth. The reviewer is puzzled by the fact that the present investigation does not discuss or even mention Margaret Fries' pioneering studies of early child development. Her observations on large groups of infants during their first 10 days of life have elucidated, inter alia, different congenital activity types and that the activity pattern of an infant probably persists throughout life. These activity patterns certainly have a bearing on the mothers' attitudes from early months on-

wards and are only one example of many factors that contribute to the complex interplay of inborn behavior characteristics and environmental influences which, e.g., lie behind infants' "irritability".

Åke Mattsson, Stockholm

David Yi-Yung Hsia: Inborn Errors of Metabolism.

Year Book Publishers, Chicago 1959, 358 pages. Numerous illustrations. Price \$ 9.50.

This is the first comprehensive survey of our current knowledge concerning all those various disorders which have been brought together under the denotation of inborn errors of metabolism. The book is written in an excellent way and contains all important features of these diseases. Particular attention has been paid to their biochemistry and pathogenesis but also to the etiology with complete discussion of the role of inheritance.

It may be predicted that this book will become the classic text-book of this type of disorders.

Rolf Zetterström, Göteborg

Heck, W. and Stoermer, J.: *Pediatrischer Ekg-Atlas*.

Georg Thieme, Stuttgart, 1959. 230 p., 181 fig. DM 78:—.

Most textbooks and manuals of electrocardiography give but little information about the electrocardiogram in infants and children. The classical work of Ziegler (1951) deals only with the normal ECG in this age-group, while the ECG-findings in various pathological conditions are discussed in the more recent textbooks of pediatric cardiology. In the present work, the first of this type in the German language, data has been collected from the ECG's in a great number of normal infants and children. On the basis of this data normal standards are presented in tables. In addition, the characteristics of the ECG including the vectorcardiogram in infants and children of different ages are pointed out. The greatest part of the book is oc-

cupied by a number of representative tracings in normal infants and children, in various kinds of rhythm disturbances and in a number of well defined pathological conditions, mostly congenital cardiac malformations. The text including the legends is lucid and well concentrated. The reproduction of the ECG's which have been taken with a direct-writing technique is very satisfactory but test markings are lacking, an omission that irritates a reader and often leaves him at bay. The volume is handy to use and will give much information to the pediatrician interested in electrocardiography.

Lars-Erik Carlgren, Göteborg

Sciacca, A. and Condorelli, M.: *Involution of the Ductus Arteriosus*.

Bibliotheca Cardiologia (S. Karger), Basel, 1960. 52 p. 25 fig. SFr 7:—.

A critical review is given of previous work dealing with the normal closure of the ductus arteriosus. The view held by a majority of authors at the present time is that involution takes place exclusively after birth, the function of the ductus being essentially the same throughout foetal life. Morphological studies carried out by the present authors show that, at least in guinea pigs, arrest of growth and beginning anatomical closure take place already before birth and that this process is not accelerated in early post-natal life. Their observations would support the earlier findings of Variot and Cailleau (1920) in human fetuses and new-born infants. The authors also studied the effect of ligation of the ductus arteriosus on, among other things, the right heart in full-term fetuses and fetuses half-way through the period of gestation. In these experiments placental circulation was intact and respiration had not been allowed to start. The operation was well tolerated by the first group but not by the latter indicating the relative unimportance of ductal flow at the time of birth. — The work is a valuable contribution to the knowledge of this interesting subject and the booklet is recommended.

Lars-Erik Carlgren

From the Paediatric Department at Kronprinsessan Lovisas Barnsjukhus, Stockholm
(Head: Professor C. Gyllenswärd)

A Study on the Onset and Prognosis of Acute Vascular Purpura (the Schönlein-Henoch Syndrome) in Children

by GÖRAN STERKY and ASTRID THILÉN

Acute vascular purpura (13, 14, 15, 28) is a disease with typical skin changes, usually showing patches of purpura. In many cases there is involvement of the joints, and also abdominal pain with or without melaena. The commonest of the more serious complications is nephropathy, the morbid anatomy and clinical manifestations of which are not fully established.

The condition was first described by Robert Willan in 1808 (21), but it was Schönlein and Henoch whose names became associated with the disease, after they had noted joint and abdominal signs in combination with purpura.

Henoch described in 1899 the occurrence of renal complications. Several studies of the disease have since been described, and follow-up investigations of patients with the Schönlein-Henoch syndrome have been carried out in different parts of the world since Gairdner's publication appeared in 1948 (21), particular attention having been paid to the risk of chronic renal damage. Two investigations have been made in Scandinavia, that of Tveterås (53) in Uppsala (1936) on a series of 38 children, with follow-up of the renal cases, and Nordmark's (41) (1957) on 105 children from Åland, not followed up.

The purpose of the present investigation has been to attempt to assess the late prognosis of acute vascular purpura in a series of Swedish children. Views concerning the late prognosis in patients with renal complications are extremely varying (17, 21, 33, 34, 42, 55). Wedgwood & Klaus (55) and Diamond (18) have stated that there is a considerable risk of chronic nephritis, even in patients showing no renal signs during the initial phase.

It would be of great value to the clinician if any early diagnostic signs could be established, with a view to detecting cases that are subsequently to develop renal signs.

The assumed but unconfirmed streptococcal aetiology of the disease is of great interest. Proof that these organisms are responsible is isolation of A- β -haemolytic streptococci (called simply streptococci in this article) at the time of appearance of symptoms, or a raised serum antistreptolysin titre (AST). The occurrence of streptococci has been reported in many series, but the antistreptolysin titre in a large series has only been investigated by Bywaters, Isdale, & Kempton (9).

Another problem has been whether those patients with renal complications

Hospital	No. of cases								
	Without renal symptoms			With renal symptoms			Total number		
	♂	♀	Total	♂	♀	Total	♂	♀	Total
KLB	24	18	42	16	2	18	40	20	60
KS	34	17	51	11	7	18	45	24	69
Sachs	7	7	14	3	0	3	10	7	17
Samariten	22	20	42	3	1	4	25	21	46
Epid.	13	13	26	4	2	6	17	15	32
Total	100	75	175	37	12	49	137	87	224

Fig. 1. Patients with acute vascular purpura (Schönlein-Henoch syndrome) at the Children's Hospitals and the Hospital for Epidemic Diseases, Stockholm, 1946-58.

had a low capacity for forming antibodies in general, since low γ -globulin values were recorded in a few cases.

Material

In order to obtain as satisfactory an answer as possible to the questions set up a large series was aimed at. The case records were therefore scrutinized of all patients aged 0-15 years treated for purpura at the 4 Stockholm children's hospitals¹ and the Hospital for Epidemic Diseases (Epid.) during the period January 1946-July 1958.

With regard in particular to the genetic aspects of the problem, 12 cases of purpura with established scarlatina were excluded, as were also all patients in whom the thrombocyte count, coagulation and bleeding times, and Quick index were abnormal.

The final series, comprising 224 patients, is explained in Fig. 1. There were 137 (61%) boys and 87 (39%) girls. Forty-nine (22%) of all patients had renal signs, the criterion being the presence of proteinuria and/or ≥ 3 red cells per viewing field on at least 2 occasions. The proportion of boys to girls among the patients with renal signs is 3:1, compared with 1.6:1 for the series as a whole: the risk of developing a renal complication is greater for boys than for girls at the 5% level of significance.

The series has been divided into 2 groups, patients with and patients without renal symptoms. Special attention has been paid

to heredity, susceptibility to infection, previous infections, and clinical and laboratory findings.

All patients were requested to attend for follow-up examination during the period October-December 1958. We have personally examined 166 of them, and satisfactory information concerning renal function has been received in a further 14 cases. One patient is living abroad, and one has died from an accident. One hundred and eighty cases (81%) were therefore available.

The follow-up examination included the taking of a detailed history and routine clinical examination with measurement of blood-pressure and laboratory tests (erythrocyte sedimentation rate, haemoglobin, white cell and differential counts, serum paper electrophoresis, serum creatinine, and urinary analysis including Addis's test).

Methods

The eosinophils were estimated per cent of white cells, and relative figures only are given. Baagoe (1958) (4) has given a normal value of 1.8%, but we have taken values $\geq 3\%$ as pathological.

Paper electrophoresis was performed with a veronal buffer, pH 8.6, stained with Ponceau Red, extracted, and read off in a

¹ (The Crown Princess Louise Children's Hospital (KLB), The Caroline Hospital (K), The Sachs Children's Hospital (Sachs), and The Samariten Children's Hospital (Samariten), of which the 2 first-named are teaching hospitals with surgical units.)

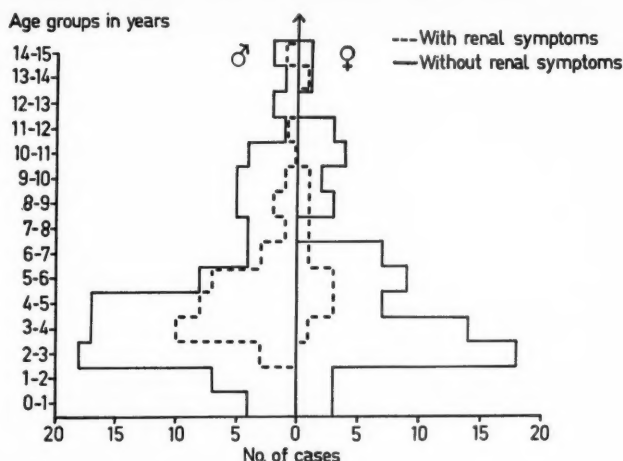


Fig. 2. Age of onset in patients with and without renal signs.

photometer. The total protein was estimated by Biuret's method (see 26).

The technique of taking nose and throat swabs for culture varied greatly. In many cases only one swab was taken, and the result of the first test has therefore been taken throughout.

In practically all cases the AST, which was usually investigated at the time of admission, was determined by the Kalbaksen technique (see 19, 29, 52). The upper limit of normal was taken as 200 I.U./ml.

An erythrocyte sedimentation rate (Westergren) of less than 15 mm in the first hour has been considered as normal.

Proteinuria during the acute stage was as a rule detected by Heller's ring test and estimated by Esbach's method. Subsequently, however, the sulphosalicylic acid method was employed, and the quantitative estimations performed by Biuret's method.

At the follow-up examination the renal function was assessed by the serum creatinin level as estimated by Jaffe's dye reaction. The normal value is 0.9-1.4 mg/100 ml.

Addis's red-cell count was employed, as it is the only reasonably reliable method of assessing persisting postnephritic urinary changes. This has been maintained by a number of authors (see Joseph & Polani, 25).

The counts were always performed by the same person, and were made the morning of sampling. More than 800,000 red cells per 12 hours has been regarded as pathological.

Results

Acute stage.

The greatest risk of developing the condition seems to be between 2 and 5 years of age, with no significant difference between the sexes or between patients with and without renal symptoms (Fig. 2).

Concerning seasonal variations, the risk is greatest during winter and early spring (Fig. 3).

In only isolated cases in our series have we found a family history of collagen disease or glomerulonephritis. L.E. cells have been searched for in a dozen or so cases, but none have been found. There were no cases with a nonspecific Wasserman reaction or positive Coombs test. Electrocardiography was carried out in 90 cases, but only one pathological result was obtained.

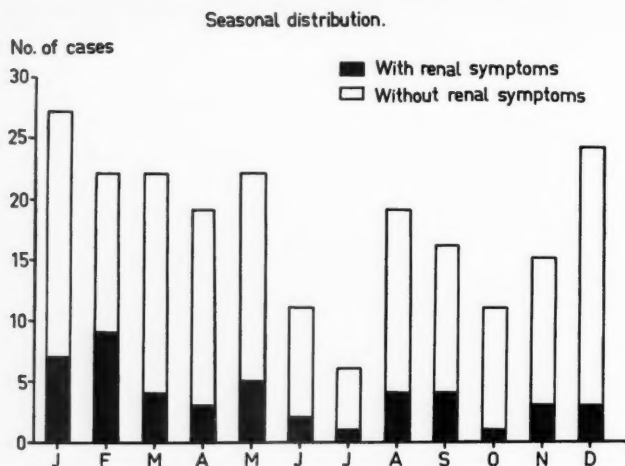


Fig. 3. Seasonal distribution.

Allergic manifestations among members of the family were reported in 45 % of the entire series, and in 35 % of patients. An allergic disposition, i.e. allergic manifestation in the patient or a relation, was present in 52 % of cases. In the original series, 46 out of 202 patients had eosinophilia of 3-5 %, and in 31 it exceeded 6 %. There were thus pathologically raised values in 38 % of the series. Food allergy was suspected in only 3 cases, but confirmation could not be obtained. Intracutaneous testing was carried out in 7 cases, with negative results. The diagnosis should not be made on the basis of this test; the patient should be put on an elimination diet, but this was not done systematically in our cases. In two or three cases small-pox vaccination may possibly have been responsible.

A history of upper respiratory infection was obtained in 75 % of the patients. Further indication of current or recent infection is a raised ESR. This was ab-

normal in 70 % of cases, but was as a rule only moderately raised. Closer investigation revealed no differences in sedimentation rate between patients with or without renal signs during the initial stage of the illness or later.

Streptococci were demonstrated in 34 % of 186 throat swabs taken on admission. Bearing in mind the possible aetiological role of this organism we have made a comparison between our findings and established streptococcal manifestations (Fig. 4), in cases of scarlatina and angina streptococcica treated during the same period at the Hospital for Epidemic Diseases. There is no direct correlation, but the incidence peaks largely correspond. The widespread use of antibiotics has of course influenced this comparison.

Another feature of fundamental importance in assessing the role of streptococci in the aetiology of the condition is the AST. The AST was determined in 113 patients, pathological findings being made

in 31 % of those patients with renal signs and in 47 % of those without. This difference appears striking, but is not statistically significant. In only 17 cases was the AST 800 or more. Repeated tests were made in 42 cases, but there was a clear increase in antibody titre in only 3 cases. Proof of streptococcal infection by demonstration of organisms, raised AST, or both, before the onset of the illness was available in 38 % of these 103 cases.

Having assumed that these patients show a poor antibody response, we attempted to establish whether they are particularly susceptible to infection, and found that 38 % could be regarded as more receptive to infection than sibs, playmates, etc.

During the first stay in hospital serum electrophoresis was undertaken in 29 cases. In all of these the α_2 was raised, but the γ -globulin value lay within the normal limits (26) except in a very few cases.

The localization and incidence of the initial symptoms and signs should provide valuable information concerning the early

Per cent of total number

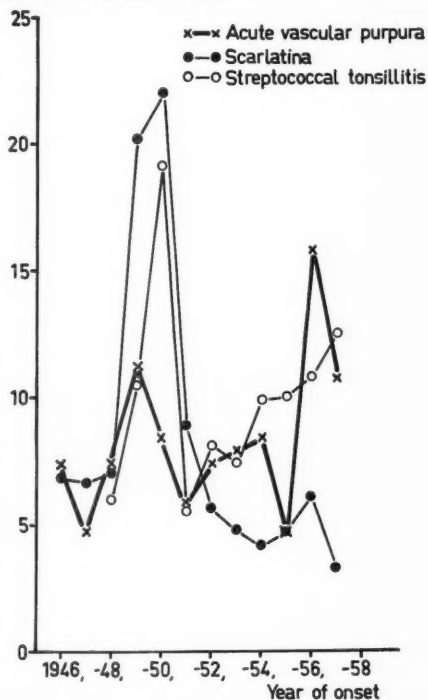


Fig. 4. Annual incidence of acute vascular purpura compared with scarlatina and streptococcal tonsillitis.

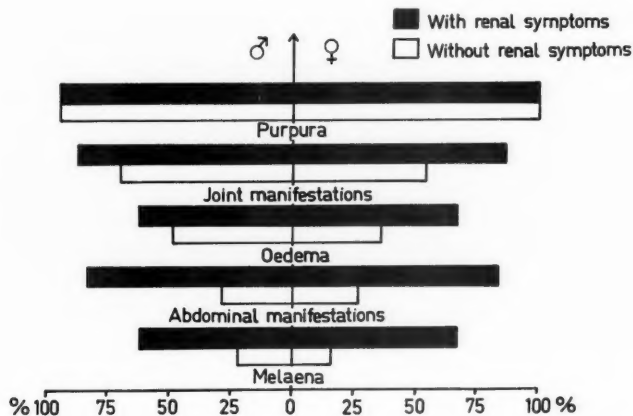


Fig. 5. Incidence of the different symptoms among patients with and without renal involvement.

prognosis. It is striking that a dramatic onset is commoner among patients who develop renal complications; and it can be seen from Fig. 5 that abdominal signs with or without melaena are commonest among patients who later show renal involvement. Owing to their marked abdominal symptoms, 10 of the patients were operated upon as acute abdominal emergencies. This also explains the fact that 2 of the hospitals (KLB and KS) are over-represented by cases with renal complications. Most of the patients have had several bouts of illness, but true recidivation (after at least one year's freedom from symptoms) occurred in only 13 cases.

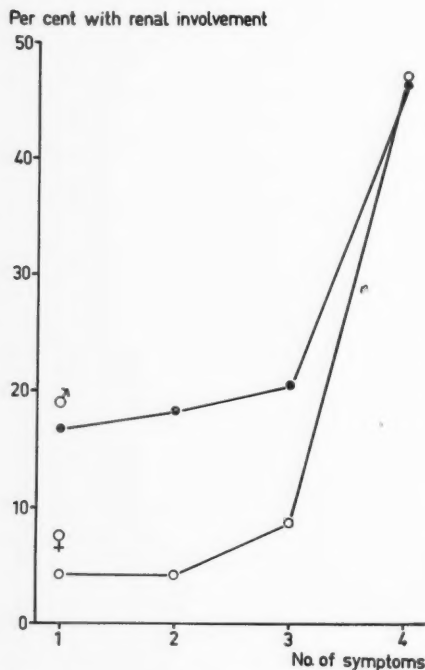


Fig. 6. Percentage risk of renal involvement among patients with purpura and 1, 2, or 3 other symptoms.

If all the symptoms and signs named in Fig. 5 are present, the risk of developing kidney disease is nearly 50 %. This is illustrated in Fig. 6, in which the risk of such complication is related to the number of symptoms.

Follow-up stage examination

Of the 180 patients followed up 83 were seen less than 5 years and 97 more than 5 years after the onset of symptoms. Of the 49 that showed renal symptoms from the start 24 were reexamined less than 5 years and 18 more than 5 years after the onset. Concerning the remaining 7, no information has been available; but all were followed up until the urine had become normal, at least temporarily. With the exception of eosinophilia and urinary changes nothing abnormal was found at follow-up examination. For example, analysis of 149 electrophoretic diagrams revealed no significant differences from a control series. There was eosinophilia in 63 % of the patients, 43 of 164 patients showing values ≥ 6 %, and 10 of these showing values ≥ 10 %.

Confirmed urinary abnormalities were present in 9 patients, and suspected abnormalities in 3 further cases, 5 and 1 respectively had initial renal symptoms. With the exception of 1 case (see below, G.B.)¹ these patients showed no initial clinical difference from other 'renal' patients. Neither during the acute phase

¹ G. B. A 9½ year-old boy who became ill with purpura, bloody diarrhoea, and massive oedema, a typical nephrotic syndrome developed within 2 days. The course of the disease was not affected by steroid therapy. The boy is now in good condition, but still has haematuria, proteinuria, and low serum albumin. Renal biopsy was performed about 1 year after the onset of the illness. For the findings and discussion of the case see Bergstrand, Bergstrand & Bucht (6).

nor at follow-up examination have any of the patients with renal symptoms shown rise in blood pressure or non-protein nitrogen, or abnormal renal-function tests (serum creatinin, endogenous creatinin clearance, water-tolerance test). As can be seen from Fig. 7, the renal signs persisted for more than 2 years in only 4 cases (observation period 2½, 2¾, 5, and 10 years). The 'nephritis' had healed after 3 months in 50 % of cases, and after 1 year in 84 %. In isolated cases the signs seem to disappear between 1 and 2 years after the onset. When they persist after 2 years, however, the damage would seem to be permanent.

All 4 patients which had no initial renal signs but who showed urinary changes at follow-up examination had had particularly long illnesses, with repeated recidivations. The same is true of the 2 cases with suspected urinary changes.

Discussion

Aetiology

The most important aetiological factor seems to be a preceding upper respiratory infection. The role played by drug and food allergy has also been discussed (1, 22, 24) and in a few cases it has not been possible to exclude small-pox vaccination (22) as the cause of the illness. Our figure of 75 % with preceding upper respiratory infection is high compared with English and American series, but tallies with another Scandinavian series (41). It also fits in with the incidence of raised ESR in the series. In 38 % of the cases the preceding upper respiratory infection seems to have been due to streptococci, as shown by positive throatswab cultures or raised AST. In assessing these findings it is

Per cent free from renal symptoms

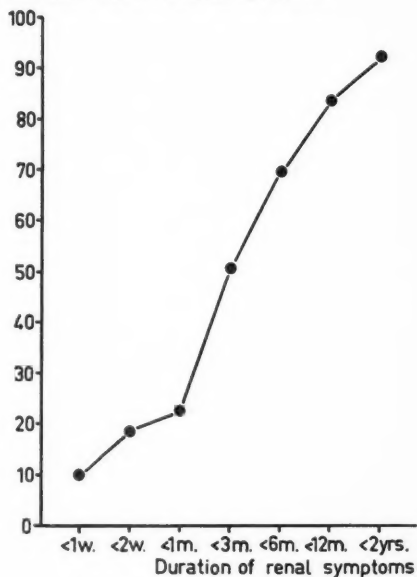


Fig. 7. Recovery rate among patients with renal symptoms.

essential to compare the situation in the rest of the population. The clinical picture in streptococcal infections varies with the age of the patient (36, 47, 48), and this further complicates the assessment. In a series from a childrens hospital in Stockholm investigated for the presence of different bacteria, streptococci were found in 19.7 % of children aged 5-47 months, and in 28.3 % of those over 48 months (30). Incidence figures of 13.3-23 % are given for other series from areas with similar climate to that prevailing here (quoted by Lagercrantz). The variations are great among different Schönlein-Henoch series, but as a rule the figures lie between 25 and 30 % (9, 16, 41). Our incidence figure of 34 % is thus only slightly higher than that for the normal

population, but tallies well with the findings of other researchers in patients with acute vascular purpura.

Concerning the AST, it would seem to be established that children in general show higher values than adults (19, 29, 52). In a series of 52 healthy children, Tunevall (1948) (52) found that 30 had an AST of 200 or more for no apparent reason; and Kalbak (quoted by Tunevall) reported in 1942 that in 16 % of a series of 99 healthy children under 16 years the AST was ≥ 200 . The normal value for single estimations is difficult to establish, partly owing to the considerable error of the method: Lagercrantz (29) arrived at an upper limit of 320 I.U./ml; but in order to be able to make comparison with other series we, like other authors (9, 19, 52), have set the upper limit of normal at 200. The correlation between a positive streptococcal culture and a pathological AST varies greatly: Tunevall reported an AST < 200 in 36 % of streptococcus-positive cases, and Packalén (43) in 27 %, and in both these investigations the throat-swabbing was carried out with particular care. Although Bywaters *et al.*, unlike other authors (quoted in 19), consider that the treatment of the preceding infection has no effect upon the AST, we have included only untreated patients. The relatively low values of AST in our series might be explained if the syndrome were only sometimes caused by streptococci, other organisms playing an important role. It is striking that in that third of the series in which the illness was 'proved' to have been due to streptococci, a rise in AST was noted in only a few cases. The reason for this may perhaps be found in the hypothesis put forward by Bywaters

et al. concerning failure of antistreptolysin synthesis in these patients, the reason for this being that the pathogenic strain of streptococcus belongs to a special group with weak antigenicity. We have not typed the streptococci in any of our cases, and have therefore been unable to test this theory. It would be most interesting, as Bywaters *et al.* have also suggested, if data could be obtained concerning other antibodies to streptococci. Support for the theory that Schönlein-Henoch patients have a defective antibody-forming capacity is obtained from the observation that these children seem to be more susceptible to infection than others. We have been unable to confirm our preliminary hypothesis that this might be reflected in the form of hypogammaglobulinæmia.

Pathogenesis

Acute vascular purpura has been regarded as a 'reaction of hypersensitivity', like 'allergic disease' and 'collagenosis' in the widest sense of the terms (13, 14, 15, 28, 49), the antigen-antibody reaction taking place in the smallest vessels. More recently, however, Dameshek and his team (13, 14, 28) and others have put forward the theory that acute vascular purpura might be due to auto-immunization to components of the vessel walls. The problem has also been approached by means of experimental investigations. Clark & Jacobs (11) and Bernard, Mathe & Israel (7) have succeeded in producing generalized vasculitis which clinically and histologically resembles the findings in Schönlein-Henoch's purpura. On the other hand, Piomelli, Mele & Stefanini (46) were unable to confirm this, but interesting similarities with the findings in collagen

diseases were found, tallying with earlier clinical observations (16, 31). The 'allergic disposition' of the patients, as was apparent from the history and the eosinophilia, is unequivocal, and this would undoubtedly support the theory that the disease is a form of 'hypersensitive reaction'. Allergic manifestations in the patient themselves were present in 35 % of our series, a considerably higher incidence than that in a comparable normal population, reported by Peltonen, Kaasanen & Peltonen in Finland to be 4.6-14.6 % (44); and the incidence of allergic manifestations in the patients and their relations seems to be higher than in other series of acute vascular purpura (12, 22).

Clinical findings

The sex distribution of the series tallies well with the findings of other authors (21, 31, 41, 53, 55), but the incidence of renal signs (22 %) is much lower than that usual in the literature, where figures of up to 90 % may be found. An explanation of the varying figures that have been given for the incidence of renal complications, which has been devoted little attention, is undoubtedly the varying composition of the series. This was pointed out by Lippman (37) as long ago as 1912. If the criterion is the presence of all symptoms making up the syndrome, the risk of developing renal complications in our series is over 50 %. The seasonal variation would seem only to reflect the general immunity, and tallies closely with that of scarlatina and acute glomerulonephritis. Owing to the assumed relationship between acute vascular purpura and different rheumatic manifestations, the ECG is of importance. The findings in our cases

accord with earlier reports (21) that cardiac involvement is rare in Schönlein-Henoch's syndrome. In adults, however, pathological ECG changes are said to be commoner (39). It is well known that the abdominal symptoms may be so severe that operation is undertaken, usually on suspicion of intussusception. The gastrointestinal lesion has been investigated by a number of authors (5), and X-ray studies have been made (23). Neurological signs indicating active intracranial 'vasculitis' or hæmorrhage are surprisingly uncommon: Lewis & Philpott (32) have reported a few such cases, however, and our series includes one. Acute vascular purpura can occur without typical skin hæmorrhages, as Schönlein and Henoch themselves pointed out. We have seen several examples of this, but all such cases were carefully excluded from the series. In one case we recorded an anti-hæmophilic globulin level (for method see 8) below the limit of normal, and further investigation of these cases with regard to the coagulation factors is therefore indicated.

Treatment

In 1948 Gairdner wrote, 'no treatment has been proved to have any effect upon the course of the illness'. As far as we know, no investigation has been carried out into the influence of bed rest upon the development of renal signs in acute vascular purpura. Investigations have been carried out with respect to glomerulonephritis, however, in which prolonged bed rest has not been shown to improve the prognosis (2, 25). Among those of our cases in whom the period of bed rest

varied no difference has been noted with regard to renal complications.

Corticosteroids have been tried in recent years, but with no proven effect except possibly in isolated cases (40, 45, 51, 53, 55). Our experience of about 20 cases has been that this treatment may be indicated when the course of the illness is very stormy, but that it does not affect its duration and prognosis.

Early prognosis

There are a few early pointers that may be of value in assessing the prognosis of the illness. Patients with abdominal symptoms and melæna, or in whom the onset is sudden, or who show several of the symptoms and signs making up the syndrome run a great risk of developing temporary or permanent renal damage; and the risk is considerably greater in boys than in girls.

Late prognosis

The prognosis of the renal lesion in acute vascular purpura has been better in this series than in most others published during recent years. After an observation period of at least 2 years, 11.4 % (4 out of 35) of the patients with initial renal signs still show pathological urinary changes.

Abnormal urinary findings were made at follow-up examination in 2.5 % (3 of 119) of the patients in whom the urine was initially normal. In that part of the series followed up for over 2 years, 7 out of 154 (4.5 %) show signs of a kidney lesion. Two years is a short observation period for the assessment of the risk of developing chronic nephritis, but we consider it not unwarranted since in no case

have we observed recovery after this period; and the figures obtained after a 5-year period are comparable.

The 'nephritis' of purpura compared with acute glomerulonephritis

The two conditions are similar in certain respects. Thus there is a preponderance of boys, a preceding upper respiratory infection is usual in both, and the urinary changes are to some extent similar. There are important differences, however, as was pointed out by Christian in 1917 (10), and subsequently by other authors (24, 31, 34, 54). The following differences are found between our series and Scandinavian series of acute glomerulonephritis (20, 27, 50). Common features of the nephritis of purpura are:

- a) There is no family history of nephritis.
- b) There is a marked allergic disposition.
- c) The onset takes place at an earlier age.
- d) The onset is often dramatic.
- e) The ESR is raised during only a short period.
- f) The AST is low.
- g) There is prolonged hæmaturia.
- h) Urinary casts, raised non-protein nitrogen, and raised blood pressure are rare.
- i) The renal clearance is normal.
- k) There is a higher frequency of persisting urinary abnormalities than in acute glomerulonephritis.

These clinical observations would seem to be confirmed by the recently published renal biopsy investigations (6, 54), which have shown that the morbid anatomy of 'purpura nephritis' is different from that of acute glomerulonephritis.

Summary

A series of 224 children with acute vascular purpura was investigated with the object of assessing the ætiology and early

and late prognosis of the condition. Sixty-one per cent were boys and 39 % girls. Twenty-two per cent had renal symptoms during the acute phase of the illness, the incidence being significantly higher in boys than in girls. Fifty-two per cent of the children had an 'allergic disposition', and 38 % were said to be abnormally susceptible to infection. There was a history of preceding upper respiratory infection in about 75 % of cases; and the ESR was moderately raised in about the same number. There was evidence that the infection was due to group A β -haemolytic streptococci (positive culture or raised AST) in only one-third of cases. It was found that there were some features that could give a clue to the early prognosis. Eighty-one per cent of the patients were followed up. Fifty per cent of those that had shown initial renal signs had normal urine 3 months later. Recovery was not observed in any patient in whom

abnormal urinary findings were present over a period of 2 years or more. Of the 35 patients followed up for this time, 4 (11.4 %) still have pathological urinary changes. In the group with normal urine during the initial stages, 2.5 % were found to have pathological urinary changes at follow-up examination after 2 years or more. The nephritis of purpura seems to differ clinically from ordinary acute glomerulonephritis. Our experience would apparently support the view that acute vascular purpura belongs to the 'collagenoses'.

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Bilirubin Studies in Premature Infants who Received Menadione Derivatives or Vitamin K₁ at Birth¹

by HOLGER DYGGVE

Introduction

Toxicological studies with vitamin-K preparations in animals

The toxicity of menadione (2-methyl-1,4-naphthoquinone), menadiol (2-methyl-1,4-naphthohydroquinone) and different esters of these substances has been found to be unequal in different animals. While 25 g/kg orally of vitamin K₁ was non toxic in mice, DL 50 was about 400 mg orally to mice of menadione and esters (Ansbacher *et al.* (3), Molitor & Robinson (22)). Pronounced haemolytic anaemia and necrotic wounds were observed in dogs receiving 7 doses of 20 mg/kg menadione subcutaneously and in rabbits when several injections of 20 mg/kg had been given (3). The disuccinate compound had a DL 50 of 100 mg/kg in rabbits and dogs (Fromherz (12)), while 5-7 subcutaneous injections of 20 mg/kg of menadione was a lethal dose for cats (3). In two of three rabbits receiving 3 intravenous injections of 5 mg menadiol per kg anaemia occurred (3). Injections of 15 mg of Synkavit per kg into dogs caused haemoglobinuria (12). The diphosphate and the disuccinate preparations produced convulsions in rabbits in which the deadly dose after intravenous injection was 100-150 mg/kg (12).

Molitor & Robinson found no anaemia in rats who had received 350 mg/kg orally of vitamin K₁ for 30 days. Zbinden *et al.* (42) gave large doses of Konaktion (vitamin K₁ as an aqueous colloidal suspension fabricated by Hoffmann-La Roche) to animals. While

no signs of haemolysis were observed after subcutaneous injection of 100 mg/kg or intravenous injection of 20 mg/kg into dogs, 100-150 mg/kg intravenously produced slight transient haemoglobinuria but no Heinz inclusion bodies. No haemolysis occurred in mice after 4×100 mg/kg i.v. of vitamin K₁ or in rats receiving 100 or 200 mg/kg intravenously. In mice 4×100 mg subcutaneously or intravenously of Konaktion produced no inclusion bodies, while after subcutaneous injections of Synkavit (menadiol-sodium-diphosphate) 4×10 mg/kg into mice more than three quarters of the erythrocytes contained Heinz-bodies. Such bodies were seen in the blood of dogs after a subcutaneous injection of 20 mg of Synkavit per kg whether the dogs were newborn or fully developed. Zbinden *et al.* found no increased osmotic or mechanical fragility of the erythrocytes when a very high proportion of these contained Heinz-bodies (experiments with mice).

Allison, Moore & Sharmann (2) found that Synkavit and other vitamin-K substitutes were much more toxic to vitamin-E deficient rats than to rats receiving a normal food. A few hours after the injection of 100 mg/kg of Synkavit haemoglobinuria and severe anaemia occurred when the rats had been on a vitamin-E deficient diet for several weeks, while only slight haemolysis without haemoglobinuria was observed in ordinarily fed rats. Two other vitamin-K substitutes were

¹ This study was aided by a grant from Hoffmann-La Roche & Co., Basel, who also supplied us with the vitamin-K preparations.

even more toxic than Synkavit causing haemoglobinuria and sometimes death in normally fed rats after the injection of 100 mg/kg. Synkavit given by mouth seemed to be harmless. Other vitamin-K preparations were less toxic and vitamin K₁ emulsion was non toxic even to vitamin-E deficient rats after the injection of 100-200 mg/kg.

Observations on the toxicity of vitamin-K preparations in man

In a patient with Laennec's cirrhosis Richards & Shapiro (29) produced transient anaemia after the injection of 12-20 mg intravenously of menadione sodium bisulfite. Intravenous injections of 4×20 mg of the same substance gave no anaemia in a normal man, but after 9×10 mg plus 5×20 mg i.v. the haemoglobin fell from 100 to 77 per cent.

Haemolytic anaemia with many Heinz inclusion bodies in the erythrocytes of premature infants was described in 1953 by Gasser (13). All his 14 prematures had received total doses of 30-170 mg of Synkavit, but since the intensity of Heinz-body formation was not always related to the timing and amount of Synkavit given, Gasser thought these bodies to be spontaneously occurring. Allison (1) and Willi (39), who have described similar cases in premature infants receiving large doses of Synkavit, were among the first to warn against large doses of water soluble vitamin-K substitutes to newborn infants. According to Willi (40) Heinz-bodies, thought to be a sign of impending disintegration of the erythrocytes, occur very often in premature infants but seldom in more than 20 per cent of the erythrocytes. In the toxic form of Heinz-body formation he found as many as 94 per cent of the red cells containing such bodies. Willi has

the opinion that immaturity of the spleen plays an important role in the spontaneous Heinz-body formation. In cases of congenital agenesis of the spleen persistent Heinz-bodies are present and in prematures with numerous Heinz-bodies the weight of the spleen was abnormally low. Allison and co-workers (2) think that the low vitamin-E level in the blood of newborn infants, causing abnormal haemolysis of their erythrocytes in vitro by hydrogen peroxide (a haemolysis which can be prevented by giving α tocopherol to the infants (György, Cogan & Rose (15)) possibly make the erythrocytes more susceptible to the haemolytic action of vitamin-K substitutes. Willi (40) could not prevent the formation of Heinz-bodies in mice by giving vitamin E subcutaneously together with Synkavit. Richards *et al.* (28) could diminish the degree of haemolysis of erythrocytes in solutions of hydrogen peroxide by the administration of vitamin E to fullborn infants, but failed to produce any significant change in concentrations of bilirubin as compared with a control group.

Increased jaundice and hyperbilirubinaemia in premature infants following rather large doses of Synkavit has been described by Bound & Telfer (4), Meyer & Angus (21), Nitsch (25), Vest (36), Samartzis & Leikin (31), Gleis (14) and Wespi (37), whereas Ströder *et al.* (35) found no difference in the serum bilirubin level whether premature infants received 10 or 1 mg of Synkavit intramuscularly (30 prematures in each group).

Bound & Telfer found the average level of indirect serum bilirubin to be 9.7 mg per cent on the fifth day of life among 51 premature infants who received 1 mg of

menadiol sodium diphosphate intramuscularly at birth—with 4 per cent of the values falling above 18 mg per cent. In 55 premature infants receiving 10 mg of the same compound intramuscularly daily for three days the average serum bilirubin level was 15.4 mg per cent and 38 per cent of the infants had values above 18 mg per cent. This group contained two infants who died with kernicterus without blood group incompatibility. Meyer & Angus also found higher serum bilirubin levels when 30 mg of Synkavit was given to premature and to a lesser degree to fullborn infants, than when no vitamin K was administered. Nitsch gave 10 mg of Synkavit to 22 premature infants and 1 mg of Konakion to 22 other premature infants. The average serum bilirubin value was 8.6 mg per cent on the fifth day in the Synkavit group and 5.9 mg per cent in the vitamin K₁ group. Vest found higher serum bilirubin values in premature infants receiving 30 mg of Synkavit than in those receiving 1 mg of Synkavit. The difference was only statistically significant on the sixth day of life. Samartzis & Leikin found the average serum bilirubin value on the fifth day to be 11.6 mg per cent in 20 premature infants receiving 1 mg of Synkavit intramuscularly. In 12 premature infants who received 10 mg of Synkavit i.m. three times the average bilirubin value was 14.0 mg per cent, but 4 of these infants received exchange transfusions because of bilirubin levels over 20 mg per cent. Nineteen premature infants receiving 25 mg of vitamin K₁ (Mephyton) intravenously had an average serum bilirubin level of 6.6 mg per cent on the fifth day. Gleis and Wespi made no bilirubin determinations but found the intensity and frequency of jaundice to be highest among premature infants respectively full-term infants who had received large doses of Synkavit. Gleis found the mortality and the incidence of kernicterus to be higher in premature infants receiving 20–70 mg of Synkavit than in a group receiving 5–10 mg of vitamin K₁. Laurance (20) reported the occurrence of kernicterus and death in six premature infants shortly after the routine dose of water-soluble vitamin K was in-

creased from 10 mg once at birth to 10 mg daily for three days. Crosse, Meyer & Gerard (5) observed that many of their cases of kernicterus in premature infants without blood group incompatibility had received large doses of Synkavit. Schall & Hüher (32) observed that the frequency of kernicterus in premature infants verified by autopsy fell from 14.7 per cent in 1953–55 when 30 mg of Hemodal was given to 4.5 per cent in 1956 when only 2 mg of the same vitamin-K substitute was administered. During the latter period the infants also received prednisolone. On the other hand Hottinger (18) found no difference in the frequency of kernicterus comparing 106 premature infants receiving 40–150 mg vitamin-K analogues and a similar number of premature infants receiving only 10–50 mg vitamin K. Rossier (30) analyzed 16 cases of kernicterus in premature infants among whom only 8 had received vitamin-K preparations. News & Norton (24) found no definite relationship between hyperbilirubinaemia or kernicterus and administration of vitamin K in their 68 premature infants. Dyggve (9) compared groups of about 100 premature infants given 10 mg of menadione sodium bisulfite or vitamin K₁ intramuscularly at birth. Among infants with birth weight between 2000 and 2500 g practically no differences were seen, whereas significantly higher levels of serum bilirubin were found in premature infants with birth weight below 2000 g, when the bisulfite compound was administered. Twenty-four per cent of the infants in this group had a maximal serum bilirubin level of 20 mg per cent or more, while only 14 per cent of the smallest premature infants receiving Konakion reached the same high level. There were about 40 infants below 2000 g in each group. Somewhat lower haemoglobin and higher reticulocyte counts were found in the bisulfite group, but these differences were not statistically significant. Willi, Vest & Käser (41) studied the influence of vitamin K₁ (Konakion) in a dose of 1 mg respectively 10 mg in premature infants. No significant differences were observed concerning prothrombin time, haemoglobin, reticulocytes, Heinz-bodies or

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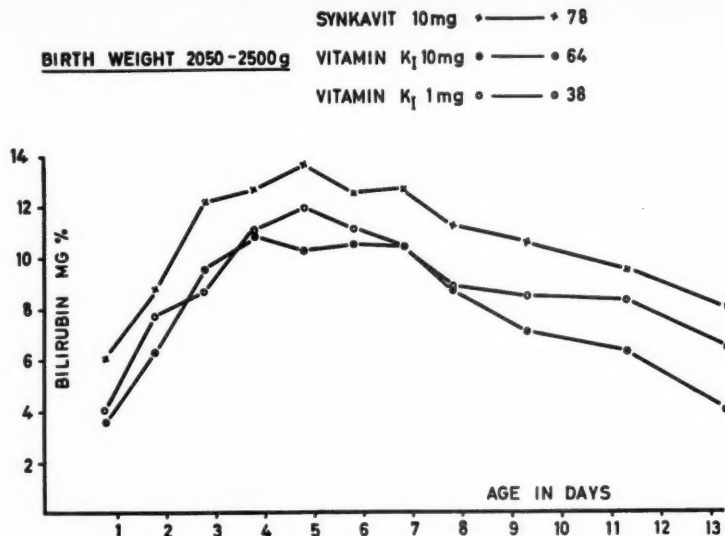


Fig. 1. Average total serum bilirubin values in premature infants with birth weight between 2000 and 2500 g. The number of infants receiving the different vitamin-K preparations is indicated on the top at the right side.

serum bilirubin—even among the infants with birth weight below 1500 g.

Material and Methods

In one of the two Obstetric Departments of the Rigshospital in Copenhagen all newborns received 1 mg or 10 mg of vitamin K₁ (Konaktion) intramuscularly immediately after birth, while in the other department all infants received 10 mg of menadiol sodium diphosphate (Synkavit) in the same manner. One hundred and thirty-five prematures received Synkavit and 40 per cent of the infants weighed 2000 g or less at birth. One hundred-nine prematures received 10 mg of Konaktion and 38 per cent of these weighed 2000 g or less. In addition 73 premature infants received 1 mg of vitamin K₁—48 per cent of these having a birth weight below 2000 g.

Blood group determination was performed in all mothers and on the umbilical cord blood of all infants. Coombs test,

Rosenfields and Munk-Andersens tests (23) were carried out in all infants and all cases of blood group sensitization were excluded from the series. Total serum bilirubin (method of With (38)), haemoglobin and reticulocyte counts were determined every other day, and the prothrombin time (method of Larsen & Plum (27)) was estimated on the third day of life and sometimes more often. Practically all the premature infants received exclusively mothers milk.

The few cases in which the mothers had received vitamin-K preparations before delivery and when the infants received more than one injection of vitamin K were excluded. No blood transfusions or exchange transfusions were given to the infants. Besides vitamin K no other medication was used except sodium penicillin, oxygen and glucose or saline in a minority of the cases. Sulfonamides, known to be able to produce Heinz-bodies and anaemia in prematures were never used. The number of haemorrhages in living and dead infants was registered during the period of examination.

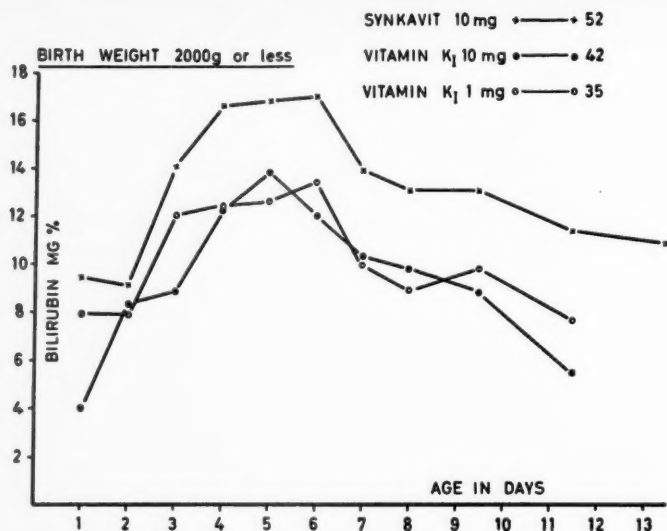


Fig. 2. Same as Fig. 1 in infants below 2000 g. The level is significantly highest in the Synkavit group.

Results

Serum bilirubin

The average total serum bilirubin values on the different days of life during the first two weeks are shown in Fig. 1 and Fig. 2.

In Fig. 1 the bilirubin curves in infants with birth weight between 2000 and 2500 g are presented. The number of infants examined is indicated on the right side at the top of the figure. No statistical difference between the values among the infants receiving 1 or 10 mg of vitamin K₁ was found, and only the values on the 9–10th day and on the 13–14th day of life in prematures receiving 10 mg of Synkavit or 10 mg of vitamin K₁ are statistically significantly higher in the former group. Among the infants weighing less than 2000 g the difference is more pronounced (Fig. 2). The average level was about 17

mg per cent from the 4th to the 6th day in infants given Synkavit, while it was only 12–13 mg per cent in those receiving Konakion. This difference is highly significant ($P < 1\%$). No constant difference was found between the bilirubin values of prematures receiving 1 or 10 mg of vitamin K₁. Since the levels were not higher in the 10 mg than in the 1 mg group no toxic influence on the serum bilirubin level was seen after 10 mg of Konakion. The number of infants with serum bilirubin values above 20 mg per cent is seen in Fig. 3.

The percentage of premature infants with serum bilirubin values of more than 20 mg per cent was twice as high in the Synkavit group as among those who received vitamin K₁. In Fig. 4 the same infants have been divided according to birth weight. One fourth of the 52 infants below 2000 g receiving 10 mg of menadiol sodium diphosphate reached bilirubin

Serum bilirubin (maximal value).

	Synkavit 10 mg	Vitamin K ₁ 1 or 10 mg	Vitamin K ₁ 10 mg	Vitamin K ₁ 1 mg
Number of infants examined	130	179	106	73
Number of infants above 20 mg %	25	17	8	9
Per cent of infants above 20 mg %	19.2 %	9.5 %	7.5 %	12.3 %

Fig. 3. Number and percentage of premature infants with maximum serum bilirubin values above 20 mg per cent.

levels above 20 mg per cent. More infants receiving 1 mg of vitamin K₁ had serum bilirubin levels above 20 mg per cent than among those who had received 10 mg of vitamin K₁. This is probably due to the fact that the groups receiving only one mg are relatively small. Great individual variation in the degree of jaundice was observed in newborn infants—the reason for this was often unexplainable. The smallest infants tended to have the highest values probably on account of immaturity of their liver function.

Haemoglobin

The average haemoglobin percentage is shown in Fig. 5 and 6. The haemoglobin

values were about equal in the three groups during the first three weeks of life. The infants receiving Synkavit had a little lower haemoglobin values during the period of examination, but the differences are statistically insignificant. In Fig. 5 it looks as if the infants receiving 1 mg of vitamin K₁ had the highest values around the 14th and 18th day, but since only 4 and 3 infants were examined in this group at that age this may be false.

In the Synkavit group two cases of severe haemolytic anaemia requiring blood transfusions occurred in a pair of twins.

The mother had had an early abortion one year before the delivery of the twins. During the last 3 weeks of pregnancy a light hypertension and albuminuria were present and

Serum bilirubin (maximal value).

Birth weight	Synkavit 10 mg	Vitamin K ₁ 1 or 10 mg	Vitamin K ₁ 10 mg	Vitamin K ₁ 1 mg
Number of infants examined				
2000-2500 g	78	102	64	38
<2000 g	52	77	42	35
Number of infants above 20 mg %				
2000-2500 g	12	8	4	4
<2000 g	13	9	4	5
Per cent of infants above 20 mg %				
2000-2500 g	15.3 %	7.8 %	6.3 %	10.5 %
<2000 g	25.0 %	11.7 %	9.5 %	14.3 %

Fig. 4. Same as Fig. 3 divided according to birth weight.

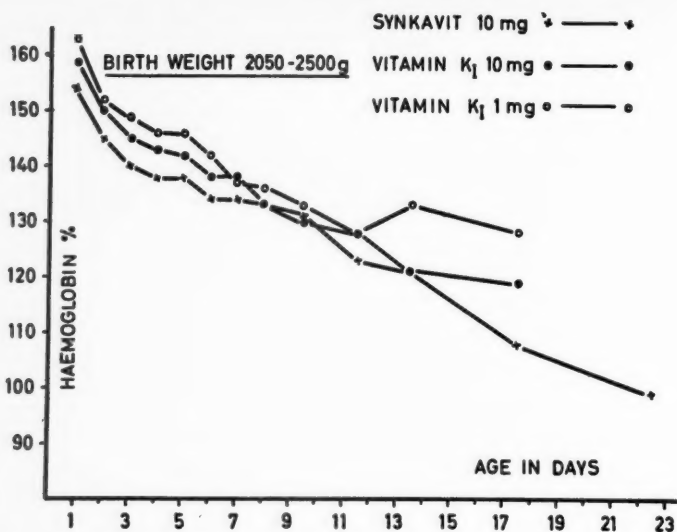


Fig. 5. Haemoglobin values. Same infants as in Fig. 1. The differences are not significant.

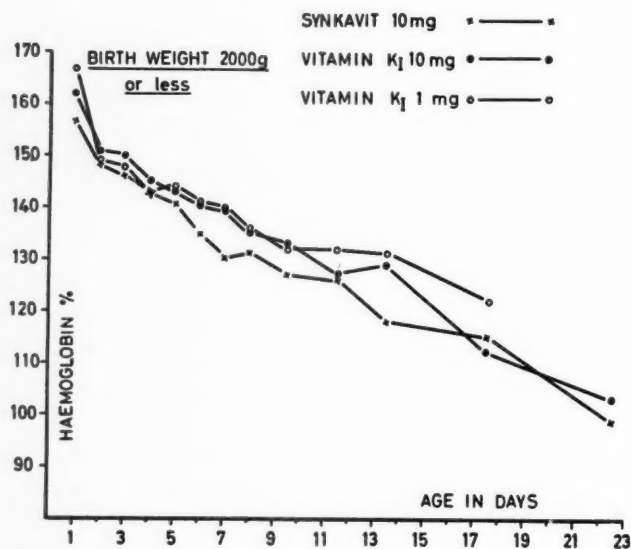


Fig. 6. Haemoglobin values. Same infants as in Fig. 2. Again no significant difference.

she was put to bed. The hypertension disappeared and the albuminuria was only slight at the time of birth, which occurred 4 weeks before term. Her Wassermann reaction was negative and the haemoglobin value was normal. The first twin (A) was delivered without difficulty in breech presentation. The infant was normal at birth and weighed 2100 g. There was only slight icterus with a maximal serum bilirubin of 8.1 mg per cent on the 5th day. On the 10th day it was 6.0 mg per cent.

Days of life	Haemo-globin %	Reticulo-cytes ‰	Blood trans-fusion (ml)
2	117	62	
5	118	60	
7	98	42	
10	90	46	
13	72	76	
15	53	102	30
16	68	68	
20	53	70	40
30	55	40	50
38	76	6	
60	64	16	
75	70	20	
151	83	16	
182	90	5	

The mother as well as both of the twins were all of blood group A Rh positive. No immune antibodies were found in the mothers serum and Coombs test was negative. The haemolysis of the erythrocytes in hypotonic saline dilutions was also normal in both twins. The clinical condition of twin A and the weight gain was satisfactory. The infants were thought to be identical twins (girls).

The second twin (B) weighed 2300 g at birth. Delivery and condition at birth was normal. Slight icterus was noted on the second day, when the serum bilirubin was 4.7 mg per cent. From the 5th to the 14th day the bilirubin value was 11–12 mg per cent and on the 22th day it was 1.2 mg per cent.

Twin B was very pale and in a bad condition on the 14th day of life with many nucleated red cells in the blood. The liver was felt 2 cm below the costal margin. Besides transfusions the infants received oral

Days of life	Haemo-globin %	Reticulo-cytes ‰	Blood trans-fusion (ml)
2	105	50	
5	105	46	
7	101	84	
10	90	150	
12	90	160	
14	21	348	50
15	59	182	40
16	70	124	
33	58	20	50
34	73		
60	60	6	
75	70	14	
151	81	12	
182	90	8	

iron therapy. They were sent home from the Paediatric Department at the age of 34 days and the further course and development was normal. Both twins could walk without support at the age of 12 months.

Reticulocytes

The number of reticulocytes per thousand erythrocytes are given in Fig. 7, showing the average of the highest count in each infant. The number was a little higher in the Synkavit group than in the vitamin-K₁ groups. By statistical evaluation of all the figures it was found that in the weight group below 2000 g the number of reticulocytes on the second, third, fifth and eighth day was significantly higher in the Synkavit than in the 10 mg Konakion group. On the other days of life, however, the difference was not significant, so that on the whole the differences are not uniform. In the groups receiving 1 or 10 mg of vitamin K₁ the average number of reticulocytes was also a little higher in the lowest weight groups than among the bigger prematures. The reticulocyte count was generally highest on the first day of life, but sometimes a rise was seen during the first or second week of life.

Reticulocyte counts.

Birth weight	Synkavit 10 mg				Vitamin K ₁ 10 mg				Vitamin K ₁ 1 mg			
	Average	Range		Number of infants	Average	Range		Number of infants	Average	Range		Number of infants
		Min.	Max.			Min.	Max.			Min.	Max.	
≥ 2500 g	42	12	182	135	29	16	134	109	30	12	90	70
2050-2500 g	38	12	182	83	26	18	90	66	24	12	72	37
≤ 2000 g	51	18	142	52	34	16	134	43	36	12	90	33

Fig. 7. Number of reticulocytes per 1000 erythrocytes. Average maximal number in the three groups divided according to birth weight. The highest counts were found in the Synkavit group.

Prothrombin time

The prothrombin time was determined, generally on the third day, with the method of Plum & Larsen (27), a micro-modification of Quicks method. Human brain thromboplastin was used. The normal adult value is 18-19 seconds with this method. No significant differences between the three groups were demonstrated. As shown in Fig. 8 the prothrombin times were on an average a little longer among the infants with the lowest birth weight, indicating that the coagulability of the blood was a little poorer in this group.

Frequency of haemorrhages

During the period of examination, lasting 15 month, 2397 liveborn infants with

a birth weight over 1000 g received 10 mg of menadione sodium bisulfite or 10 mg of menadiol sodium diphosphate (Group A). Group B receiving 10 mg of vitamin K₁ comprised 2942 infants (about 700 of these infants received only 1 mg of vitamin K₁). The total number of considerable haemorrhages in living infants and in those dying during the stay in the Hospital (autopsy was performed in practically all infants who died) was 34 or 1.42 per cent in Group A (receiving water-soluble vitamin-K substitutes) and 43 or 1.46 per cent in Group B (receiving vitamin K₁). The haemorrhages shown in the table were observed.

No difference between the frequency of haemorrhages in the two groups was found.

Prothrombin time (third day of life).

Birth weight	Synkavit 10 mg		Vitamin K ₁ 10 mg		Vitamin K ₁ 1 mg	
	Average (seconds)	Number of infants	Average (seconds)	Number of infants	Average (seconds)	Number of infants
≥ 2500 g	42	134	37	99	41	70
2050-2500 g	40	82	36	60	40	37
≤ 2000 g	45	52	38.5	39	42	33

Fig. 8. Prothrombin times. The differences are not significant. The range of the values was between 20 and 91 seconds. The normal adult value is 18-19 seconds with the method employed.

	Group A	Per thousand	Group B	Per thousand
Melena	2	0,83	4	1,36
Kephalhae- matoma	15	6,25	18	6,12
Intracranial (dead)	10	4,17	13	4,42
Intracranial (living)	4	1,67	5	1,64
Adrenal	3	1,25	2	0,68
Intraabdomi- nal	0	—	1	0,34
Total	34	14,17	43	14,56

Discussion

The total serum bilirubin level was significantly higher among prematures with birth weight below 2000 g receiving 10 mg menadiol sodium diphosphate than in those receiving vitamin K₁. All the other differences found between the three groups of prematures were not statistically significant, but a tendency towards lower haemoglobin values and higher reticulocyte counts was observed in the Synkavit group. The average prothrombin time on the third day of life was almost the same whether the infants received 10 mg of Synkavit or 1 or 10 mg of vitamin K₁.

The only authors who have compared the serum bilirubin values in prematures receiving 10 mg of Synkavit and those receiving 1 mg of Synkavit or 1 mg of vitamin K₁ are Ströder *et al.* (35), who found no difference, and Nitsch (25) who found a somewhat higher bilirubin level among the infants receiving Synkavit. Nitsch does not mention the birth weight in his two groups of prematures.

Neonatal icterus is more marked in premature than in fullborn infants and the main factor in the genesis of neonatal jaundice is the limited excretion of bilirubin by the liver (19). Since the serum bilirubin level of premature infants is

often very high, and since a rather high proportion of these infants have respiratory difficulties and hypoxia, which in my opinion favor the development of bilirubin encephalopathy, all drugs able to augment the bilirubinaemia should be abandoned. It is probable, but not certain, that one or two mg of the water-soluble vitamin-K substitutes can be given without risk. From the data presented here and the work of Willi, Vest & Käser (41) and that of Samartzis & Leikin (31) it seems that injections of aqueous suspensions of vitamin K₁ are harmless to premature infants in a dose of 10 or even 25 mg. On the other hand we know from the investigations of Hardwicke (16) and of Sells, Walker & Owen (34) that the daily dose necessary to prevent a drop in the prothrombin activity of newborn infants is only 2-5 micrograms. Since the prothrombin time in premature infants receiving 1 or 10 mg of vitamin K₁ were equal, a dose of 1 mg seems to be sufficient. This dose can be repeated without risk in cases with bleeding and diminished coagulability of the blood.

The severe anaemia of the twins who had received 10 mg of Synkavit was probably caused by this drug. It is interesting, however, that Willi *et al.* have described somewhat similar symptoms in two triplets, with birth weight 800 and 1120 g, who had received Konakion.

Different authors have found the action of vitamin K₁ to be more potent than that of vitamin-K substitutes. It is well known that vitamin K₁ is far more active than the substitutes in the treatment of haemorrhages caused by hypoprothrombinaemia and lack of proconvertin (Factor VII) in patients who have received too big

doses of dicumarol or other anticoagulants. Dam & Søndergaard (6) found a faster action of vitamin K₁ in vitamin-K deficient chicks than of Synkavit. Haupt & Krebs (17), Scheier (33) and Willi (39) found a better action of Konaktion than of Synkavit upon the prothrombin (and proconvertin) level of newborn infants, but Dyggve, Dam & Søndergaard (11) found no faster or better action of vitamin K₁ than of Synkavit on the prothrombin time after intravenous injection to newborns with greatly prolonged prothrombin times.

That the frequency of haemorrhages in the newborn can be diminished by prophylactic administration of vitamin K either to the mother before delivery or to the infant just after birth has been shown among others by Dyggve (7, see also Plum *et al.* (26)). I recommend the prophylactic oral administration of vitamin K to the mother for some days before delivery, since many haemorrhages begin during and shortly after birth, and since I found the prothrombin and proconvertin levels at birth to be higher in antenatally treated than in untreated infants (8). The prothrombin time of the infants were not shorter when the mothers had received vitamin K₁ than when Synkavit was administered ante partum (10). If no vitamin K has been given to the mother 24-4 hours before birth, and in cases of

complicated delivery, asphyxia neonatorum and in premature infants vitamin K should be given directly to the infant.

Summary

Total serum bilirubin, haemoglobin values and reticuloocyte counts were determined in 317 premature infants receiving different vitamin-K preparations intramuscularly at birth. One hundred and thirty-five of these premature received 10 mg of the tetra-sodium salt of 2-methyl-1,4-naphthohydroquinone diphosphate (Synkavit). One hundred-nine received 10 mg of an aqueous suspension of vitamin K₁ (Konaktion) and 73 one mg of Konaktion.

The number of premature infants with serum bilirubin values above 20 mg per cent was twice as high in the Synkavit group as among those receiving vitamin K₁.

No significant differences were found concerning haemoglobin values, reticuloocyte counts, prothrombin times or number of haemorrhages.

Since hyperbilirubinaemia was previously observed among premature infants who had received 10 mg of menadione sodium bisulfite, it seems preferable to use vitamin K₁ in premature infants instead of water-soluble substitutes with vitamin-K activity.

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The Prognosis in Diabetes with Onset before Age Two

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The purpose of the present study has been to examine the prognosis for diabetics with very early onset, their growth and development, achievements, mortality and complications. A larger survey of the prognosis in diabetes with onset before age 2 does not seem to have been published before.

Material and Methods

Among the 3847 juvenile diabetics treated at the Joslin Clinic from January 1922, the first year in which insulin was used, up to the end of 1956, 118 had onset before age 2 (3.1%). Of these 118 there were 13 with onset before age one, that is to say 0.34% of the total group of juvenile diabetic patients treated during the same period. The earliest discovery of the disease was at the age of 7 weeks (glycosuria and hyperglycemia discovered during pneumonia in another hospital). Fifty-eight of the 118 were boys and 60 girls. There were 6 boys and 7 girls with onset before age one. Familial occurrence of diabetes was found in 51% of the cases. All the patients have not been continuously under treatment at the clinic. Several cases have been seen only intermittently, a few only once or twice. Fifty-four were re-examined in 1956 and 1957, questionnaires were sent to other patients previously known to be alive. All eye examinations were undertaken by a certified ophthalmologist. Where examinations of

calcifications were made, the examinations included the abdominal aorta, the arteries of the pelvis and legs.

Present age and duration

At the end of 1956 20 were dead, of whom 3 had onset below age one. Seventy-three were alive, 25 were not traced.

Table 1 summarizes the age and duration of the 73 living patients. The age of the patients varied from 2-36 years and the duration from 1-34 years. Twenty-eight had survived 20 years' duration of disease, among them 9 had more than 30 years' duration. In 1957 the oldest patient had his 37th birthday and had survived 35 years of diabetes.

Growth and development.

Achievements

The height in the females 20 years of age or more varied between 134-175 cm. The average was 161.3 cm, a figure which tallies well with the average 161.4 cm found by Ohlson *et al.* (1955) in Ohio women between 17-21 years of age. Eleven per cent of the females were below 152 cm.

The height in the males 20 years or more varied between 124-182 cm with an average of 167.8 cm. This figure is 7 cm below the average 174.8 cm found by White (1955) in white American army

¹In receipt of a Fulbright travel grant and grant from The American Association of University Women 1956-1957.

TABLE 1. *Present age and duration (73 cases).*

Age in years							
0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
3	14	9	15	6	12	10	4
Duration in years							
0-4	5-9	10-14	15-19	20-24	25-29	30-34	35-39
8	12	12	13	4	15	9	

TABLE 2. *Age and duration at death (20 cases).*

Age in years at death						
0-4	5-9	10-14	15-19	20-24	25-29	30-35
7	1	2	5	2	1	2
Duration in years at death						
0-4	5-9	10-14	15-19	20-24	25-29	30-35
7	2	2	5	1	1	2

men. Nineteen per cent of the males were below 160 cm. One male was below 130 cm. Five of the 118 patients were feeble-minded. Two of the 5 were also epileptics. The rest did not seem to have presented gross intellectual disturbances, many had higher education. The oldest was a Ph. D. and professor in an American university. One patient was an assistant director of a large firm.

Twenty-four were married and 15 had children of their own. The only one with onset before age one who has had children, had a spontaneous delivery after 23 years' duration.

The degree of control

Estimated after the Joslin groups' standard (Wilson, Root & Marble 1951) the control seems to have been fair-good in 60 % of the cases before 10 years' duration and poor in 40 %, between 10-14 years' duration fair-good in 53 %, poor in 47 %, between 15-19 years' duration fair-

good in 30 %, poor in 70 % and after 20 years' duration fair-good in 40 %, poor in 60 %.

Mortality and complications

The age and duration at death in the 20 fatal cases are listed in Table 2. One patient died at discovery of disease 4 months of age. The age at death in the other cases varied from 2-34 years and the duration from 1-33 years. More than a third of the fatalities (7 cases) had occurred before 5 years of age and duration. The chief causes of death have so far been infections (7 cases) and coma (6 cases) accounting for more than half of the deaths (see Table 3). Pneumonia accounted for

TABLE 3. *Causes of death (20 cases).*

Infections	7
Coma	6
Vascular complications	3
Hypoglycemia	1
Suicidium	1
Unknown	2

TABLE 4. *Total incidence of vascular lesions by age.*

Age years	Albumin (Examined)	%	Hypertension (Examined)	%	Retinitis all types (Examined)	%	Retinitis proliferans (Examined)	%	Calcified arteries (Examined)	%
5-9	(77)	0	(77)	0	(5)	0	0	0	(9)	0
10-14	(60)	0	(60)	0	(20)	10	(20)	0	(25)	0
15-19	(46)	2.2	(46)	0	(21)	14.3	(21)	4.8	(22)	9.1
20-24	(29)	6.1	(29)	0	(19)	68.4	(19)	15.8	(20)	30
25-29	(23)	39.1	(23)	13	(21)	85.8	(21)	28.7	(21)	66.7
30-34	(9)	44.4	(9)	22.2	(6)	100	(6)	16.7	(9)	77.8

3 deaths, tuberculosis, whooping cough, otitis media and encephalitis one each. No death from coma has occurred since 1948 and no death from infection since 1954.

Degenerative vascular complications. Only 3 patients had so far died of degenerative vascular complications, 2 of kidney- and 1 of combined kidney and heart lesion. The age at death in these cases varied between 26 and 34 years with an average of 30 years. The average duration at death was 29 years. The incidence of degenerative vascular complications by age and duration is seen in Table 4 and 5. The figures in these tables show the numbers examined in different age groups during several years, not only the figures by the last examination in 1956 and 1957. Among the 9 patients whose eye grounds were examined before 10 years of age and

duration, 2 showed mild degree of retinopathy. One of them was a case of Morquio disease, the other one was a patient who showed one single microaneurysm during treatment with cortisone. Between 10-14 years' duration 10% of those examined showed retinopathy, between 15-19 23%, between 20-24 68% and between 25-29 79%. After 30 years' duration 100% showed retinitis. Retinitis proliferans was not discovered before age 18, after 17 years' duration. The peak of incidence of retinitis proliferans was between 25-29 years' duration when 31.6% of the examined showed retinitis proliferans. After 30 years' duration the incidence was less, 25%. However, the number examined in the group with 30-34 years' duration was only 4.

Seven of the whole group with onset before age 2 are known to have become blind

TABLE 5. *Total incidence of vascular lesion by duration.*

Duration years	Albumin (Examined)	%	Hypertension (Examined)	%	Retinitis all types (Examined)	%	Retinitis proliferans (Examined)	%	Calcified arteries (Examined)	%
5-9	(73)	0	(73)	0	(9)	22.2	(9)	0	(12)	0
10-14	(59)	0	(59)	0	(20)	10	(20)	0	(25)	0
15-19	(46)	4.3	(46)	0	(22)	22.7	(22)	4.5	(22)	9.1
20-24	(29)	13.8	(29)	0	(19)	68.4	(19)	15.8	(22)	27.3
25-29	(20)	40	(20)	15	(19)	78.9	(19)	31.6	(19)	78.9
30-34	(8)	50	(8)	25	(4)	100	(4)	25	(18)	87.5

TABLE 6. *Total incidence of vascular lesions by duration (White (1956)).*

Duration years	Albumin per cent	Blood pressure per cent	Retinitis per cent	Retinitis proliferans per cent	Calcified arteries per cent
0-4	0.8	0.5	0	0	0
5-9	1.5	1.2	2.5	0	1.7
10-14	7	4.5	19	3	14
15-19	18	15	59	18	44
20-24	41	32	82	47	73
25-29	39	44	88	46	88
30-34	44	53	93	59	94
35-39	63	70			

in one or both eyes because of retinitis proliferans or retinitis proliferans complicated by gross retinal hemorrhages. The youngest who became blind was 20 years old, after 19 years' duration, the previously mentioned patient with retinitis proliferans. Only one has become blind after 30 years' duration.

The earliest finding of calcifications was at age 18, after 17 years' duration. Before 20 years' duration only 2 of the examined showed calcifications. After 20 years' duration only 2 of the examined were free from calcifications.

Significant proteinuria not related to other diseases than diabetes was not discovered before age 18, after 17 years' duration and only in one case before age 20, that is to say an incidence of 4.3 % between 15-19 years' duration. The previously mentioned patient with retinitis proliferans also had proteinuria when she was 18 years old. Between 20-24 years' duration the incidence of proteinuria was 13.8 %, between 25-29 40 % and between 30-34 50 %.

Significant hypertension was not discovered before age 20. At 25 years' duration only one of the examined was free from vascular complications. None of those

examined after 30 years' duration was entirely free from vascular complications.

The patient with the earliest onset of nephropathy and blindness belonged to the poor control group. She had been on a free diet until the first examination at the Joslin Clinic 18 years of age when she was discovered to have retinitis proliferans and proteinuria. The single patient who was free from vascular complications at 25 years' duration belonged to the good control group. He was a doctor and the son of a doctor.

A striking feature has been the varying course of the degenerative vascular complications. A patient in whom retinopathy was discovered at age 14 after 13 years' duration has shown little signs of progression during the past 13 years. One patient with fair-good control, 32 years old at the last examination, has had proteinuria for eight years without other clinical signs of nephropathy, that is to say normal blood pressure, normal serum nonprotein nitrogen and normal values of cholesterol. During these 8 years he has had minimal retinal changes and no signs of calcification of the arteries of the legs and pelvis or of the aorta. The patient who has survived 35 years' duration of the disease

has had roentgenological calcifications for 9 years, mild degree of retinopathy for 12 years but still no signs of nephropathy. On the other hand a patient who died from Kimmelstiel Wilson syndrome at 25 years' duration of diabetes did not reveal significant proteinuria at an examination 2 years before death.

Neuropathy. Five patients have developed slight but definite signs of neuropathy but not before age 18. The previously mentioned patient with proteinuria and retinitis proliferans also had neuropathy at age 18 and was a case of diabetic triopathy.

Epilepsy. Proved cases of epilepsy with convulsions or attacks of unconsciousness without relation to hypoglycemia has been found in 7 out of the whole group of 118 patients, an incidence of 6%.

Other complications. Five of the 118 diabetics have had pulmonary tuberculosis. Other serious complications which may be related to diabetes have not occurred.

Five patients have presented enlargement of the thyroid gland. No case of thyreotoxicosis or myxedema have been discovered.

Discussion

In the present material the problems of growth and development have largely solved themselves as stated by White in her material of juvenile diabetics in 1956.

The incidence of epilepsy (6%) seems rather high. Further investigation of this problem including electroencephalographic studies of the patients is needed.

The varying course of the degenerative vascular complications has also been

mentioned in other series. Thus White (1956) has reported that there is increasing evidence of the fact that a certain number of juveniles shows a stationary status of their vascular complications. Beetham (1957) has mentioned the varying course of retinitis proliferans in a mixed group of diabetics with onset both in childhood and in later life.

Even if the number examined in the different age groups in the present material is small, it is striking that there is a smaller incidence of degenerative vascular complications before 30-35 years' duration of diabetes than in White & Wascow's material and in Whites's from 1956 (see Table 5). These two series consisting of juvenile diabetics treated at the same clinic and with different ages of onset before 15 and with mixed types of control may seem appropriate for comparison.

It is also striking in the present material that diabetic nephropathy and roentgenological calcifications of the arteries have not been found before age 18, after 17 years' duration.

It has been stressed before that diabetic nephropathy rarely occurs before age 15 or before puberty, among others by Fanconi, Botsztejn & Kousmine, Skouby and White. In most of the juvenile diabetic patients the kidney lesion seems to have been the last of the degenerative vascular complications to cause clinical symptoms. The absence of signs of nephropathy before age 15 in follow-up studies which include few patients with very early onset may be due to the circumstance that the disease has not been of sufficient duration for the development of nephropathy at this age. However,

in Fanconi and associates' series there were at least 7 diabetics with onset before age 10, of whom 2 with onset before age 5. Some of the other patients in the material with onset between age 10-15 developed nephropathy already after 4 years of diabetes. After 16 years' duration all had clinical signs of nephropathy, and after 21 years they were all dead except one. These results Fanconi and associates believed were caused by the patients' diet which was poor in carbohydrates and proteins and rich in fat. Onset of puberty seemed to accelerate the occurrence of vascular complications.

It does not seem justified to believe that the absence of signs of nephropathy before age 18 in the present material is due only to an appropriate diet as the control seems to have been poor in about 50 % before 15 years' duration. This finding as well as the rare occurrence before age 15 stated by other investigators may seem to suggest that some additional pathogenetic factor (or factors) develops at or after puberty. The lack of calcifications

of the arteries before age 18 in the present material and the rare occurrence before age 20 stated by White may seem to support the same theory.

Summary

A follow up study of 118 diabetics with onset of disease before age 2 is presented. Twenty of them were known to have died up to the end of 1956, 73 were alive, 25 were not traced.

The incidence of the degenerative vascular complications before 30-34 years' duration was less than in other follow up studies of juvenile diabetics from the same clinic with different ages of onset before 15 and with mixed types of control.

Signs of nephropathy not related to other diseases and retinitis proliferans were not seen before 17 years of diabetes. Roentgenological calcification of the arteries were not found before 17 years' duration. These findings may seem to suggest that some additional pathogenetic factor (or factors) develops at or after puberty.

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On the Incidence of Haemolytic Disease of the Newborn due to ABO Incompatibility

by HOLGER DYGGVE and GEORG MUNK-ANDERSEN

As early as 1944 it was shown by Halbrecht (8) that haemolytic disease of the newborn due to ABO incompatibility could not be a rare disease, since 95 per cent of the newborn infants who developed jaundice during the first days of life ("icterus praecox" in contradistinction to "physiological" jaundice) were ABO incompatible with their mothers. He found the incidence of "icterus praecox" due to ABO incompatibility to be 0.6 per cent. Halbrecht's findings (8, 9) were confirmed by Wiener, Sonn & Hurst (25) and later by others. Hsia & Gellis (10), for instance, found an incidence of 0.7 per cent, Turman, Vaughan & Shelly (23) 0.86 per cent, and Valentine (24) 1.4 per cent.

The main difficulty in diagnosing the individual cases of "ABO haemolytic disease" has been the lack of a simple test for demonstrating antibody on the newborn infant's red blood cells. The anti-globulin test described by Coombs, Mourant & Race (3) in 1946, which is invaluable in demonstrating Rhesus sensitization, usually fails in cases of A or B sensitization.

In such cases better results seem to be obtained with the test advocated by Witebsky *et al.* (26). In this test, which is best performed on slides, it is investigated whether the infant's erythrocytes agglutinate when suspended in serum (or plasma) from a normal adult person. Zuelzer & Kaplan (29) found it to be positive in 22 out of 35 cases, whereas in the hands of Shumway, Miller & Young (22) it was positive in 8 out of 9 cases of ABO haemolytic disease. Gunson (7), who found the test positive in 24 out of 27 similar cases, demonstrated that the chances of a positive result were greatest when the red blood cells were obtained during the first 24 hours of life.

An even more sensitive test seems to be the Rosenfield modification of Coombs' test. Rosenfield (21) obtained a positive reaction in 39 cases (2.6 per cent) of 1480 cord bloods from unselected infants. All 39 proved to be ABO incompatible with their mothers. A similar sensitivity has been shown by the conglutination test described by Munk-Andersen in 1956 (13). This test was positive in 35 cases (2.0 per

cent) of 1700 unselected cord bloods (15). According to David & Ingrand (4) this test was positive in 96 out of 100 cases of ABO haemolytic disease.

Material and Methods

In the present study the Rosenfield antiglobulin test and the Munk-Andersen conglutination test were used concurrently as screen tests on 3500 unselected cord bloods from infants born in the Obstetric Departments of the University Hospital, Copenhagen, during the period April 1, 1957 to April 1, 1958. For both tests, we used the same saline suspension of red cells washed four times.

Rosenfield's test (20) was performed in duplicate, using two different, highly avid antiglobulin sera in the dilutions optimal for demonstrating Rh sensitization. Two drops of Coombs serum dilution were added to 2 drops of a ca 5 per cent red blood cell suspension in a test tube, immediately centrifuged at 2000 r.p.m. for 10 seconds. The results were read macroscopically and microscopically, and if about 20 per cent of the cells formed agglutinates of 3 or more red cells, the reaction was considered positive.

Munk-Andersen's conglutination test (13) was performed on a slide. One drop of the colloidal medium containing dextran was added to 1 drop of about 5 per cent red cell suspension. The mixture was stirred to make a round field with a diameter of about 18 mm, tilted and rolled slowly for 10 minutes so that the fluid made a circular movement. Macroscopic reading at the end of 10 minutes. This test too was carried out in duplicate in most cases, using two different colloidal media containing different dextran preparations. One medium contained: Dextran Pharmacia DRI 204 5 per cent (wv), NaCl 1.3 per cent (wv), and AB serum 25 per cent (vv), the values for dextran and NaCl indicating g per 100 ml of prepared medium, whereas the value for AB serum indicates ml per 100 ml prepared medium. The other medium contained

dextran Pharmacia DRI 226 5 per cent, NaCl 1.3 per cent, and AB serum 10 per cent. The latter dextran gave stronger reactions than the former, but it was more apt to give non-specific reactions. This tendency could be counteracted by reducing the content of AB serum in the prepared medium to 10 per cent.

In cases where an infant's erythrocytes gave positive reaction in the Rosenfield or the conglutination test or in both, elution of antibody from the infant's cells was done and the specificity of the antibody investigated. To packed red cell sediment washed three times was added saline, equal parts, the suspension was heated at 56°C for 10 minutes, centrifuged in 56°C warm centrifuge buckets, and the supernatant saline, the eluate, immediately removed by a pipette. This eluate was then incubated for an hour with A₁, B, and O cells from adults and the incubated red blood cells investigated for antibody sensitization, by the Rosenfield test as well as the conglutination test. To this end, we used the latter of the two dextran solutions (containing dextran DRI 226). To control non-specific reactions incubation of the same blood cells in saline solution was used.

The serum of the sensitized babies was studied for free, incomplete ABO antibody acting upon red cells of the infant's own blood group, and the maternal serum was titrated for complete as well as incomplete anti-A and anti-B using the colloidal medium with dextran (DRI 204). The same titration was carried out following "partial neutralization" of the maternal sera by equal parts of saliva from a Group A₁B person who was secretor of AB substance (for technique cf. Munk-Andersen (14)).

Total serum bilirubin was determined by With's micromodification (27) of Jendressik & Grof's method. In addition to the serum bilirubin and haemoglobin levels, reticulocyte counts were done on the infants' bloods every other day.

Results

Among the 3500 infants studied we found 71 (2 per cent) whose red blood cells were sensitized by ABO antibody demonstrable by one or by both methods. In 28 cases positive reactions were found with both methods. In 18 cases the Rosenfield test was negative, whereas the conglutination test was positive, and in the remaining 25 cases the Rosenfield test was positive, whereas the conglutination test was negative.

In 5 cases the Rosenfield test gave a non-specific reaction, i.e. reaction in ABO compatible cases in which no other form of maternal iso-immunization could be demonstrated. By the conglutination test non-specific reactions were found in 9 cases.

Out of the 71 infants sensitized with ABO antibody 60 were A infants of O mothers, whereas 11 were B infants of O mothers.

In 69 of the 71 cases elution studies were carried out. In 67 of these 69 cases antibody could be eluted from the infant's erythrocytes, so that it could be demonstrated with certainty that anti-A or anti-B was present on the infant's red cells. In 14 instances, the eluted antibody gave cross reaction, i.e. to A as well as B cells, but not to O cells.

Sixty-one infants sera were studied for free antibody directed against the baby's own cells, i.e. anti-A in A babies and anti-B in B babies. Such an antibody was demonstrated in 60 cases.

All the maternal sera contained immune, incomplete anti-A or anti-B, but no other immune antibodies acting upon the infant cells.

As for other maternal data, it may be mentioned that 2 of the 71 mothers had mild albuminuria at the time of delivery, but no other abnormalities were found. None of them had diabetes mellitus. In the entire series there were 38 diabetic mothers, but none of them bore children sensitized by anti-A or anti-B (cf. Zetterström, Strindberg & Arnhold (28) who found that 5 out of 29 infants of diabetic mothers had ABO haemolytic disease).

About one-third of the mothers were primiparae. Eleven had a history of abortion, 5 of repeated abortions. Five had a history of stillbirths. None of the elder siblings of the newborn babies were suffering from the sequelae of kernicterus. It must be mentioned, however, that we have not personally examined these children.

Three babies were delivered by Caesarean section, 4 by forceps, and 2 were breech presentations. One infant had extrasystoles (which have later disappeared), but aside from that there were no complicating diseases of note.

The sex ratio was not unusual, 36 of the 71 babies being boys and 35 girls.

Mortality. The smallest babies, weighing 850 and 1120 g at birth, were in a poor condition and cyanosed all the time, dying on the 2nd or 3rd day of life without any visible jaundice. Both proved to have widespread atelectases and one also large haematomas in the cerebral ventricles. An immunization was probably not the decisive cause of death.

The birth weight is given in Fig. 1 which shows that 13 per cent weighed 2500 g or less, whereas the normal incidence of premature infants in Denmark is 5-6 per cent. In the Obstetric Departments of the

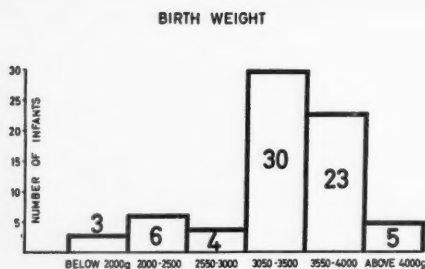


Fig. 1. Number of infants in different birth weight groups among 71 infants with ABO incompatibility.

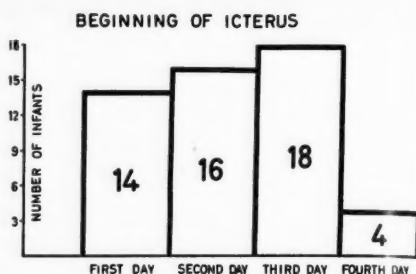


Fig. 3. Day of onset of icterus among the 52 jaundiced infants.

University Hospital, however, the incidence is 13-14 per cent.

Fig. 2 sets out the *weight loss*. In 28 per cent there was a weight loss of 200 g or over, which is considerably in excess of the usual weight loss. More than one-third had not attained their birth weight when they were discharged, generally at the age of 10 days. Most of these babies were still jaundiced on discharge.

The time of *onset of the jaundice* may be seen from Fig. 3. Nineteen were not visibly jaundiced. Out of all the babies 42 per cent became jaundiced within the first two days of life, and in 58 per cent of the jaundiced babies the icterus was noticed within 48 hours after birth.

The *severity of the jaundice* is shown in Fig. 4. Three-quarters of the babies were

jaundiced and one-third deeply jaundiced. As a rule, the jaundice lasted for 8-14 days, persisting for more than 3 weeks in only 2 cases.

Fig. 5 sets out the average serum bilirubin levels on the 1st, 2nd, 3rd day of life, etc. By way of comparison, we have plotted the levels for 150 full-term infants whose red blood cells were not demonstrably sensitized by an antibody. The levels are clearly higher in the ABO sensitized babies. There was no significant difference between the bilirubin levels in babies sensitized by anti-A and in those sensitized by anti-B. The explanation of the apparent increase in the mean serum bilirubin after the 9th day of life is that the mildly jaundiced babies are generally discharged at that time.

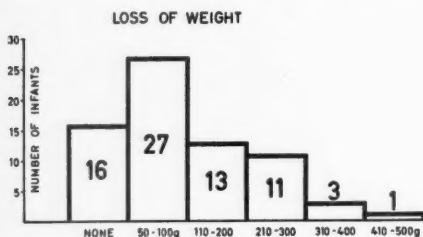


Fig. 2. Distribution of the same infants according to loss of weight during the neonatal period.

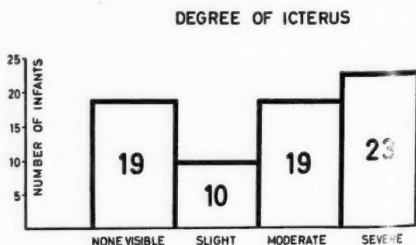


Fig. 4. Number of infants with different degrees of icterus.

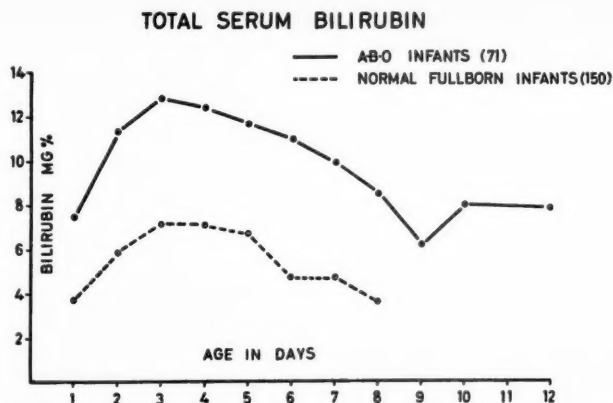


Fig. 5. Average serum bilirubin values among 71 infants with ABO incompatibility and among 150 controls. The reason for the apparent rise in the serum bilirubin level among the ABO infants on the tenth day of life, is due to the fact that only infants who were still jaundiced remained in the hospital at that time.

Thirty-four babies—or about 50 per cent—had a maximum bilirubin level of 15 mg per 100 ml or over. Eleven exceeded 20 mg per 100 ml. The mean value of the maximum serum bilirubin in all 71 infants was 12.9 mg per cent, whereas the corresponding mean value in the controls was 8.6 mg per cent. The 14 babies sensitized by cross-reacting ABO antibody showed a mean value of maximum serum bilirubin of 12.6 mg per cent.

Table 1 gives a comparison of the Rosenfield test and the Munk-Andersen conglutination test within groups of infants with different maximum serum bilirubin levels. In the group of babies whose serum bilirubin did not exceed 10 mg per 100 ml, the two methods were coincident in only one-quarter of the cases. In the other groups, the methods were coincident in half the cases, whereas 25 per cent were demonstrable only by the

TABLE 1. Result of Rosenfield's test and Munk-Andersen's test in babies grouped according to maximum serum bilirubin level.

	Maximum bilirubin level in baby's serum				The two greatly premature infants	Total
	Up to 10 mg per 100 ml	11-15 mg per 100 ml	16-20 mg per 100 ml	More than 20 mg per 100 ml		
Rosenf. test neg.						
Munk-A. test pos.	7	1	5	4	1	18
Rosenf. test pos.						
Munk-A. test pos.	7	4	10	6	1	28
Rosenf. test pos.						
Munk-A. test neg.	15	4	5	1	0	25
Total	29	9	20	11	2	71

TABLE 2. Mean maternal titre for incomplete, homologous antibody within the individual groups of newborn infants, classified according to the infants' maximum serum bilirubin levels. (Titre expressed as number of tubes with positive reaction.)

	Maximum level of bilirubin in infant's serum			
	Up to 10 mg per 100 ml	11-15 mg per 100 ml	16-20 mg per 100 ml	More than 20 mg per 100 ml
Mean maternal antibody titre	10.8	11.3	12.7	13.2

Rosenfield test and the last 25 per cent only by the conglutination test.

Table 2 shows that the higher the maximum serum bilirubin among the infants, the higher the average titre for incomplete homologous antibody in the mother (i.e. anti-A in mothers of A infants and anti-B in mothers of B infants). The titre is expressed as the number of tubes with positive reaction.

Lastly, it may be mentioned that among infants with a maximum serum bilirubin of up to 10 mg per cent, the mean titre of free, incomplete antibody was 2.3, whereas that in infants with a serum bilirubin exceeding 10 mg per cent was 3.3.

According to Fig. 6 the haemoglobin levels were lower in the sensitized babies

than in the controls. Severe anaemia requiring blood transfusion did not occur. A number of the babies had a haemoglobin level of 60 to 70 per cent a month or two after birth, but it rose during iron medication.

The average reticulocyte count was 31 per thousand in the "ABO infants" as compared with 20 per thousand in the controls. The osmotic fragility of the red cells was determined in only 5 infants in whom it was slightly elevated.

Seven had hepato- or splenomegaly. None had evident signs of kernicterus during the neonatal period. Some of the most severely jaundiced babies were lethargic and sucked torpidly, but in most cases only for a few days.

HAEMOGLOBIN

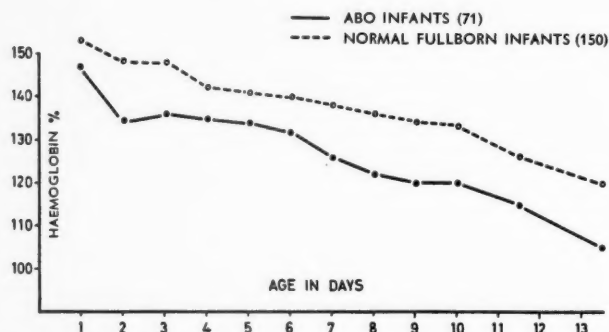


Fig. 6. Average haemoglobin values among ABO and control infants.

Only 2 had exchange transfusions of group O blood to which was added AB substance, and the jaundice yielded completely within 5 or 6 days.

Although it is too early to assess the development and prognosis at long sight, it may be mentioned that 21 of the most severely jaundiced babies have been followed up for at least 6 months after birth. One appears to be suffering from sequelae of kernicterus, whereas the others have developed normally.

Discussion

The two methods used for demonstrating ABO sensitization of newborn infants' red cells, the Rosenfield antiglobulin test and the Munk-Andersen conglutination test, appear to be only partially coincident. Incongruities appear to be most marked in the presence of a low serum bilirubin, i.e. in babies without clinical signs of sensitization. Out of the 40 infants whose maximum serum bilirubin exceeded 10 mg per 100 ml 20 showed a positive result by both methods, whereas the antibody sensitization was demonstrable only by the Rosenfield test in 10 and only by the Munk-Andersen test in the remaining 10. This indicates that as far as possible, both tests should be performed.

Since stillbirth, severe anaemia, or hydrops foetalis appear to be rare complications of ABO haemolytic disease, the main object of the treatment is to prevent the occurrence of kernicterus. It is true that only a small proportion of the cases develop kernicterus (Halbrecht (9)), but still kernicterus due to ABO incompatibility has been reported many times, *int. al.* by Wiener, Sonn & Hurst (25), Grum-

bach & Gasser (6), Polayes & McNally (18), Boorman, Dodd & Trinick (2), Reepmaker & van Loghem (19), and Zuelzer & Kaplan (29). We shall not dwell on the clinical signs of kernicterus, but merely mention that if the damage to the brain does not involve vital centres, so that it leads to death a few days after birth, the baby may survive with permanent symptoms, in particular oligophrenia or motor disturbances, especially athetosis (Perlstein (16), Evans & Polani (5), Plum (17)).

Kernicterus may be effectively prevented by exchange transfusion during the first 24 hours of life (Allen, Diamond & Vaughan (1)). Kernicterus does not appear to occur at a serum bilirubin level lower than about 20 mg per cent (Mollison & Cutbush (11)). Prematurity predisposes to kernicterus (Mollison & Walker (12)).

In our series, exchange transfusion was performed in two cases, but probably it ought to have been carried out more often. If a serum bilirubin level exceeding 20 mg per 100 ml had been taken as an indication for exchange transfusion, this procedure ought to have been done in 11 cases, i.e. in 0.3 per cent. By way of comparison, Rosenfield (21) has reported that at the Mount Sinai Hospital, New York, exchange transfusion for ABO haemolytic disease was performed in 6 cases out of 4096 infants (0.15 per cent) or half as often as exchange transfusion for Rh incompatibility which was done in 12 cases.

Summary

Cord bloods from 3500 unselected newborn infants were screen tested for ABO sensitization by two methods, Rosenfield's modification of the Coombs test and

Munk-Andersen's conglutination test. In a total of 71 infants (2 per cent) the red blood cells were found to be sensitized by ABO antibody. The two methods are only partially coincident. The ABO sensitization was confirmed by elution studies.

One-third of the infants developed severe jaundice.

The mean serum bilirubin levels were higher than in a control series. A correlation was found between the maximum serum bilirubin levels and the strength of

the maternal incomplete antibody. The babies' haemoglobin levels were on an average lower and the reticulocyte counts higher than in a control series.

Two infants were treated by exchange transfusion. Signs of kernicterus during the neonatal period did not occur, but one baby later developed signs indicating the sequelae of kernicterus.

We recommend a more active treatment by exchange transfusion than that used in the present series.

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Observations on the Urinary Excretion of Amino Acids by the Premature Infant

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The higher level of excretion of total free alpha amino acid nitrogen by the premature infant as compared to the full term infant, the older child and the adult has been noted and reaffirmed on a number of occasions (3, 4, 5, 10, 16). Relatively few observations, however, have been made on the constituent amino acids. In part this is a consequence of the hitherto cumbersome nature of column chromatography, so that reports to date by this, the most accurate technique, relate only to four 24 hour estimations on premature infants during the first three months after birth. These figures show a considerable divergence, but because of the small numbers, it is not possible to discern to what extent this may relate to age or diet or indeed to the daily variance in individual excretion. In a more extensive study where the amino acids were assayed, as in this case, by the visual comparison of paper chromatograms against standards (16) only untimed urine voidings were collected and the results were expressed in terms of an arbitrary amount of crea-

tinine. Such an index may be questioned in the light of recent studies (3) on serial urine voidings from premature infants of the same age, taken into a time flow fraction collector, which have shown that the urinary creatinine excretion coefficient is exceedingly inconstant, and, moreover, unrelated in single voidings to the free alpha amino nitrogen. Finally in a study where both urine and serum amino acid chromatograms were quantitated by planimetry, and which was designed primarily to determine the clearances of individual amino acids, random samples were again taken and again there was a substantial variance in individual results (10).

The present study was designed to minimise the potential variations arising from untimed sampling by assembling 24-hour urine collections into weekly pools for the first 8 weeks of life. In this way it was hoped to obtain a more accurate

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evaluation of the amino-aciduria of the premature infant and its normal variation.

Clinical Material and Methods

Eleven healthy premature infants whose birth weights ranged from 1020 g to 1410 g were placed on a metabolic frame in the first few hours after birth for the continuous collection of all urine. Subsequently they were fed on conventional amounts of a half skimmed milk and carbohydrate mixture. The 24-hour urine collections for the fourth day were taken as representative of the first week. Thereafter weekly pools were prepared by combining one tenth of each 24-hour collection for the second to eighth weeks of life. These specimens were stored in the freezer to await analysis. The urine creatinine was measured by the Jaffe reaction after ether extraction of interfering chromogens (15), the total nitrogen by a micro-Kjeldahl procedure, and the free alpha amino acid nitrogen by a modification of the copper method after elution from a Dowex 50 column (12). Finally individual amino acids were estimated on desalted urine by visual comparison of the ninhydrin stained chro-

matograms against a series of standards. The two-dimensional solvent systems employed were those of phenol/butanol:acetic acid and methanol:pyridine/tertiary butanol: methylethylketone:diethylamine (6, 8). The advantage in this duplication lay in the greater overall resolution of the chromatographic spots in that tryptophane and valine, glycine and serine, and histidine and lysine which were difficult to distinguish on the phenol/butanol:acetic acid system resolved distinctly on the other one.

The degree of accuracy of the visual assessment was examined on prepared chromatograms of alanine, glycine, glutamic acid, threonine and proline and found to have a mean coefficient of variation of 32%. This figure compared well enough with that for elution which was 31%, but indicates none the less that both of these two methods are essentially semi-quantitative. However, in spite of the potential variation of this method the mean total of amino acid nitrogen estimated from the chromatograms was 86% of the total amino acid nitrogen by the copper method. This is an improvement on one previous study (10) where a recovery of only 59% was achieved; but is still less exact than column chromatography (4, 5).

TABLE 1. *The urinary excretion of free amino nitrogen, creatinine and total nitrogen.*
mgm/kg/24 hrs.

Age in weeks →	I	II	III	IV	V	VI	VII	VIII	
Amino N	5.2 1.4-13.3 > 50 8.3	9.5 2.9-20.0 > 50 9.1	9.8 3.7-14.5 33 8.9	14.4 4.9-24 40 9.9	13.6 4.7-24 38 9.6	15.8 11.2-26 29 11.0	16.0 9.4-26 32 11.1	15.7 5.1-28 > 50 13.0	mean range v mean
Creatinine	4.8-13.8 > 50 121	5.2-16.1 11 148	7.3-13.3 23 153	7.8-14.4 15 170	3.3-14.8 39 173	6.6-14.3 23 221	4.5-15.2 31 280	9.4-19.6 33 333	range v mean
Total nitrogen	56-206 42 5.2	92-328 48 7.6	83-219 27 6.8	96-300 39 9.0	129-201 30 8.1	186-260 27 7.0	140-431 38 6.3	143-610 46 4.1	mean range v mean
Amino N	0.7-7.5 > 50 0.9	0.9-14.0 38 1.2	3.5-11.6 43 1.2	4.7-14.9 39 1.5	3.6-16.5 47 1.5	4.3-10.4 28 1.5	2.3-15.7 > 50 1.6	1.3-6.8 > 50 1.1	range v mean
Amino N	0.5-1.6 > 50	0.2-1.9 > 50	0.4-2.6 > 50	0.6-3.0 47	1.0-2.1 27	1.1-2.2 33	0.6-2.5 37	0.4-1.7 > 50	range v

v = coefficient of variation as %

TABLE 2. *The urinary excretion of 15 free amino acids and glutamine.* $\mu\text{mols/kg/24 hrs.}$

Age in weeks \rightarrow	I	II	III	IV	V	VI	VII	VIII
Alanine	17	35	68	74	65	76	81	95
Glycine	94	114	152	156	196	209	136	205
Threonine	18	31	65	71	59	77	65	81
Serine	42	36	44	46	60	55	66	94
Glutamine	22	19	23	18	13	33	13	11
Glutamic acid	7	31	48	41	48	48	57	55
Histidine	21	30	56	63	77	79	84	85
Tyrosine	13	30	38	40	49	49	60	66
Tryptophane	2	12	25	13	24	20	27	26
Aspartic	13	15	14	28	12	24	11	21
Valine	2	9	9	11	10	12	17	18
Leucine and isoleucine	6	18	34	23	28	32	33	30
Proline	21	50	90	83	110	133	148	136
HO proline	12	22	31	33	46	43	43	29
Methyl glycine	9	22	57	55	74	75	90	81
Cystine	7	7	7	9	8	15	8	9

Results and Discussion

The mean values for the excretion of the major components of urine nitrogen are set out in Table 1 and show a steadily increasing progression throughout the period of the study, which was in turn related to an increasing nitrogen intake. Underlying these trends in the means there was a substantial range in all these excretion coefficients (mg/kg/24 hrs) between infants, with the corresponding coefficients of variation

$$\left(\frac{\text{Standard deviation} \times 100}{\text{mean.}} \right)$$

in many instances exceeding 50%. It might have been anticipated with this wide variance (Table 3) in the excretion of total free alpha amino nitrogen that the individual components of this fraction (Table 2) would follow suite, and this proved to be the case in spite of the uniformity of the sampling and the appa-

rent trend of mean values in step with other components of urine nitrogen. As far as could be estimated these variations transcended the inherent limitations of the technique and not only were they present between individual infants but between succeeding weeks in the same infant. It was not possible to detect particular groupings or relationships between amino acids in the excretory pattern, indeed the excretion of individual amino acids seemed to be ranged haphazardly around the means in any one sample. Such variations have been observed in all studies to date on amino acid excretion in the premature infant as set out in Table 4, and for these reasons it is important to accept reservedly dogmas on such matters as individual amino acid clearances until there has been some extension of the results from column chromatography in this age group.

Notwithstanding the above variations there were certain unmistakably charac-

TABLE 3. *The excretion of free & amino nitrogen in the premature infant according to various authors.*

Author	Method	No. of infants	Free & amino N excretions	Age of infants	Diet
mgm/kg/day					
Fowler et al. ⁵	Gasometric				
	Ninhydrin-CO ₂	1	11.1	3 days	Cow's milk formula
"	"	1	8.3	67 days	
"	"	1	6.8	150 days	
Dustin et al. ⁶	Column chromatography	1	4.3	38 days	Breast-fed
"	"	1	19.4	18 wks.	Breast-fed
Sereni et al. ⁴	Gasometric				
	Ninhydrin CO ₂	5	5.0	6-16 wks.	Evap. or cow's milk
"	"	7	8.9	17-28 wks.	Evap. or cow's milk
Childs ²	Gasometric	14 Prem.	8.5	3 days to	
	Ninhydrin	& F.T.	(1.8-32.2)	3 months	Not stated
Present authors	Dowex 50 elution		12.5	4 days to	
	then copper method	11	(5.2-16.0)	8 weeks	Evap. milk

TABLE 4. *The range in the urinary excretion of 10 free amino acids in premature infants according to various authors.*

Authors →	Present authors	Sereni et al. ⁴	Fowler et al. ⁵	Dustin et al. ⁶	Schreier and Pluckthun ⁷
No. of cases	10	7	1	1	4
Age →	6 wks	28-51 days	67 days	38 days	Not stated
Body wt. in kg.	1.48-2.13	2.04-2.36	3.26	1.25	Not stated
Diet →	Cow's milk	Cow's milk	Cow's milk	Breast milk	Breast milk
Method of assay	Paper chrom. visual	Paper chrom. planimetry	Column chrom.	Column chrom.	Micro-biological
μmols/kg/24 hrs					μmols/24 hrs
Alanine	76	45	46	18	—
	31-199	10-121			
Glycine	209	92	59	101	—
	118-442	49-325			
Threonine	77	24	19	53	—
	0-173	6-33			
Glutamic acid	48	29	5.3	7.7	—
	10-189	0-81			
Histidine	79	78 mean	38	9.1	54
	9-118	30-167 range			52-56
Tyrosine	49	15	21	12.6	7.2
	24-95	0-41			2.3-9.4
Valine	12	8	—	1.8	23
	0-35	0-18			17-27
Leucine & isoleucine	32	15	8.5	7.7	15
	0-58	4-31			10-17
Proline	133	44	+	18	—
	70-238	0-95			
Cystine	15	47	3.1	8.1	54
	0-21	18-81			33-67

teristic features in the chromatograms from these infants. In the first place all of them showed a spot that had the same R_f value and gave the same colour with ninhydrin as methyl glycine. The presence of this substance has been previously considered (16) and rejected in favour of beta amino-iso-butyric acid on the basis of the rate of colour development with ninhydrin, the two having the same R_f value in p.cresol and collidine:lutidine. However in the phenol/butanol:acetic acid system beta amino-iso-butyric acid and methyl glycine move quite distinctly and the identification therefore seems valid. Whether the presence of methyl glycine in these relatively large amounts could reflect some immaturity in the synthesis (2) or possibly an ability to deamidinate creatine can only be speculation.

The second notable feature in the chromatograms was the uniform presence of free proline and hydroxyproline. Neither of these amino acids can normally be detected in this way in the urine of healthy children or adults, nor in the case of hydroxyproline in the full term infant over a month old (5). It is perhaps significant that not only were proline and glycine quantitatively the most important amino acids but that together with hydroxyproline these three amino acids make up over 40% of human collagen (11). This excess of free hydroxyproline in the urine is clearly unlikely to be dietary and might

therefore arise by a substantial increase in synthesis from ornithine or glutamic acid (13). The simultaneously high rate of proline excretion would be in accord with this. An alternative possibility assuming that collagen has a low turnover in the infant as in the adult (14), is that the free hydroxyproline and proline arise within the body from the breakdown of pre-collagen peptides (7, 17), which an immature metabolism has either created in excess or unsuccessfully incorporated into collagen.

Conclusions

1. Serial weekly pools of 24 hour urine collections from a group of 11 healthy premature infants for the first 8 weeks of life were assayed for total nitrogen, creatinine, total free alpha amino acid nitrogen, and for individual amino acids by paper chromatography.

2. The mean excretion coefficients of all measured components of urine nitrogen rose steadily during the study. Individual measurements however showed wide variations between individuals, between different weeks in the same individual and in the ratios between the components themselves.

3. The consistent presence of methyl glycine and hydroxyproline in the urine chromatograms is noted and the possible significance discussed.

Observations sur l'excrétion urinaire des acides aminés chez les prématurés

Chaque semaine, l'urine de 24 heures d'un groupe de prématurés sains fut recueillie pendant les huit premières semaines de la vie de ces

prématurés. Ceci fut fait afin d'obtenir la dose totale d'azote, de créatinine, d'acide aminotérique alpha et la dose individuelle d'acides aminés par chromatographie sur papier. Le faible coefficient d'excrétion de tous les composants de

l'azote de l'urine mesurés augmenta régulièrement au cours de l'étude. Cependant les dosages individuels, montrent de très grandes différences entre les individus et au cours des différentes semaines de la vie d'un même individu, et entre les rapports des composants eux-mêmes. On remarque la présence conséquente de méthyle glycine et d'hydroxyproline dans les chromatogrammes de l'urine et on discute la signification possible de ce fait.

Beobachtungen über die Ausscheidung von Aminosäuren im Urin bei Frühgeburten

Mittels Papierchromatographie wurden Wochenserien von Sammlungen des Urins, der jeweils in 24 Stunden von jedem Kind einer Gruppe von 11 gesunden Frühgeburten ausgeschieden worden war, während der ersten 8 Lebenswochen dieser Kinder untersucht, um den Gesamtstickstoff, das Kreatinin, den gesamten freien Alpha-aminosäurestickstoff, sowie die einzelnen Aminosäuren zu bestimmen. Der mittlere Ausscheidungskoeffizient aller gemessenen Bestandteile des Urinstickstoffs stieg während der Beobachtungen ständig an. Individuelle Messungen zeigten jedoch große Abweichungen unter den einzelnen Kindern, zwischen verschiedenen

Wochen bei demselben Individuum und in den Verhältnissen der Bestandteile untereinander. Es wird auf das ständige Auftreten von Methylglyzin und Hydroxyprolin in den Urinchromatogrammen hingewiesen und die mögliche Bedeutung dieses Phänomens diskutiert.

Observaciones sobre la excreción urinaria de aminoácidos por el lactante prematuro

Se examinaron — mediante cromatografía de papel — series semanales de colecciones de orina, producida en 24 horas, por cada uno de un grupo de 11 lactantes prematuros sanos, durante las primeras 8 semanas de vida, para determinar el nitrógeno total, la creatinina, el nitrógeno total libre alfaaminoácido y los aminoácidos aislados. El coeficiente medio, de la excreción de todos los componentes medidos del nitrógeno urinario, subió constantemente durante el transcurso del estudio. Las mediciones individuales, no obstante, mostraron amplias variaciones entre los niños, entre diferentes semanas para el mismo individuo y en las proporciones entre los componentes mismos. Se remarca la presencia constante de metilglicina e hidroxiprolina en los cromatogramas de la orina y se discute la posible significación de este fenómeno.

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Asthmatic Symptoms in the First Year of Life

by PER SELANDER

Introduction

If asthma is defined as a condition with recurrent attacks of dyspnea, which are primarily expiratory and are attended by wheezing and a short, dry cough, then the disease occurs in the very youngest ages. Actually it seems to be most common there. Thus, for example, Bray reports that among 1390 cases of asthma arising during the first decade 22 per cent commenced in the first year of life, 17 per cent in the second, and 13 per cent in the third. In an investigation of Rowe & Rowe it is stated that asthma usually began at the age of 16 to 26 months. In a Danish study of 338 children with bronchial asthma in the age of 0 to 14 years, of whom 298 could be found again, 15 per cent had become asthmatic during the first year of life, whereas the start of the disease culminated during the second and third year with 20 and 20 per cent respectively (Winge Flensburg).

The asthmatic symptoms in these youngest children have the character of an acute infectious disease and are diagnosed most often as bronchitis asthmatica or asthmatoïdes. An examination by Winge Flensburg et al. of 450 asthmatic children in the age of 0 to 14 years showed that in the age group 0 to 2 years only 7 per cent exhibited positive cutaneous reac-

tions to substances of protein nature, whereas 80 to 90 per cent of the asthmatic children over 6 years of age exhibited such reactions. These two circumstances, acute infection and negative cutaneous reaction, make it questionable whether the asthmatic symptoms in the youngest have other prerequisites for their occurrence than similar symptoms in older children and adults.

Case Material

All children in the age of 0 to 15 years with asthmatic symptoms, who were treated in the Flensburg Children's Hospital during the period 1949 to 1958, have been reviewed with regard to the age of the onset of the disease, sex, and the infants in addition with regard to temperature, sedimentation rate, white blood cell count and weight. All together there are 1092 children.

One hundred thirty nine children, who in the age of 0 to 1 year were admitted for asthmatic ailments and are now 6 to 11 years old, have been questioned regarding hereditary disposition to asthma and eczema, continued asthmatic symptoms, occurrence of eczema and hay fever, and frequent upper respiratory infections. Of these children 113 could be located. The same procedure was carried out with 119 children now in the age of 6 to 11 years who had been treated at the Hospital for genuine bronchial asthma. Of these children 111 could be located. Finally, a control group of 150 children, now

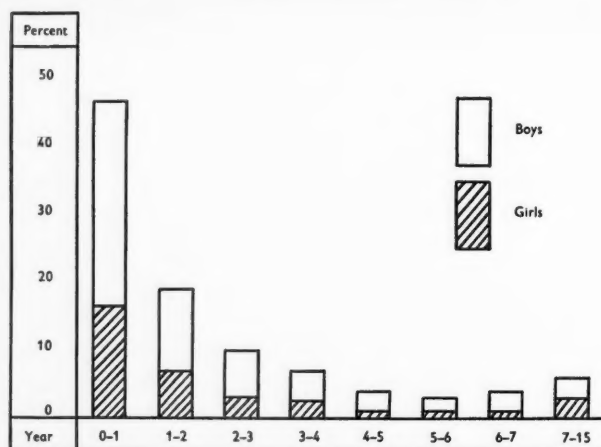


Fig. 1. The age of the first occurrence of asthmatic symptoms in 1092 children 0 to 15 years old and the frequency of boys and girls in each age group.

6 to 11 years old, was selected. These children had been treated in the Hospital for acute dyspepsia in infancy. Of these 140 could be located.

Results

From Fig. 1 it is seen that 47 per cent of the 1092 asthmatic children exhibited

the first symptoms already in infancy. In 87 per cent of the children the symptoms occurred before 5 years of age.

Boys comprise 63 per cent of the children. This sexual distribution is practically constant up to the age of 7 years, whereupon the risk of becoming ill for boys is not greater than for girls.

TABLE I. *Bronchial asthma and eczema in the heredity of 111 children in the age of 6 to 11 years who have or have had bronchial asthma, of 113 children of the same age who have had asthmatic symptoms in infancy, and of 140 children of the same age who have had acute dyspepsia in infancy, as well as some diseases these children have had.*

Diseases Children in the age of 6–11 years	Hereditary					Diseases the child has or has had							
	Bronchial asthma		Eczema			Bronchial asthma		Eczema		Hay fever		Frequent resp. inf.	
	No.	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Bronchial asthma	111	60	54.0 ± 4.73	28	25.2 ± 4.12	—	—	34	30.6 ± 4.37	14	12.6 ± 3.13	44	39.6 ± 4.64
Asthmatic symptoms in infancy	113	24	21.4 ± 3.87	20	17.9 ± 3.62	22	19.6 ± 3.76	12	10.7 ± 2.92	5	4.5 ± 1.49	30	26.8 ± 4.13
Acute dyspepsia in infancy	140	21	15.1 ± 3.03	13	9.4 ± 2.47	5	3.6 ± 1.58	8	5.8 ± 1.98	0	0	39	27.3 ± 3.79

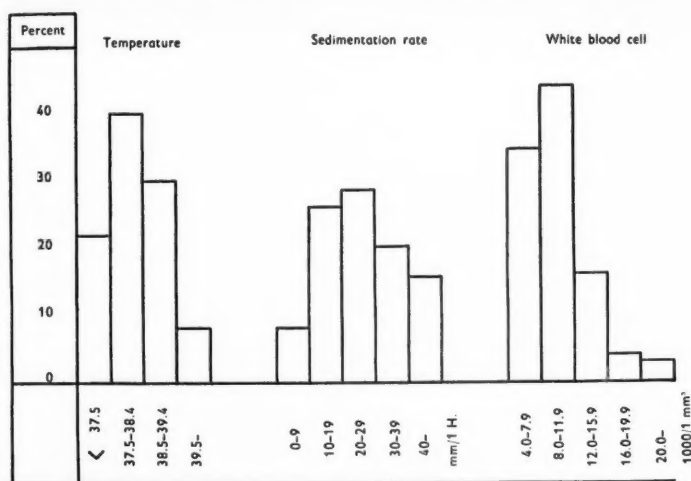


Fig. 2. The temperature, sedimentation rate and white blood cell count at the onset of asthmatic symptoms in 500 infants.

Table 1 shows that genuine bronchial asthma occurs hereditarily in somewhat higher per cent in the 6 to 11-year-olds who have had asthmatic symptoms in infancy than in those who have had acute dyspepsia in infancy. The difference, however, is not certain ($\text{Diff. } 6.3 \pm 4.92\%$). There is also a higher per cent of eczema in the heredity of children with asthmatic symptoms in infancy compared with the control cases, but this difference is not either statistically certain ($\text{Diff. } 8.5 \pm 4.38\%$). On the other hand, there is a certain difference between asthma in the heredity of genuinely asthmatic children and those who in infancy have had asthmatic symptoms ($\text{Diff. } 32.6 \pm 6.11\%$).

The table shows also that children who have had asthmatic symptoms in infancy run a greater risk of developing genuine bronchial asthma ($\text{Diff. } 16.0 \pm 4.07\%$). There is also a higher risk of developing

eczema, but this difference is not statistically certain ($\text{Diff. } 4.9 \pm 3.52\%$). The risk that these children may develop hay fever is also greater. On the other hand, they do not run a greater risk of developing upper respiratory infections.

Throughout Table 1 it is seen that children with asthmatic symptoms in infancy (bronchitis asthmatoïdes) form at the age of 6 to 11 years a group between children of the same age with bronchial asthma and the controls regarding heredity to asthma and eczema and the risk of developing eczema and hay fever. They have also an increased risk of developing genuine asthma but not of developing catarrhal infections.

Fig. 2 shows that in infants with asthmatic symptoms the temperature is obviously elevated (above 38.4) in 38 per cent, the sedimentation rate is obviously elevated (above 19 mm micro SR) in 64 per cent, while there is a definite increase

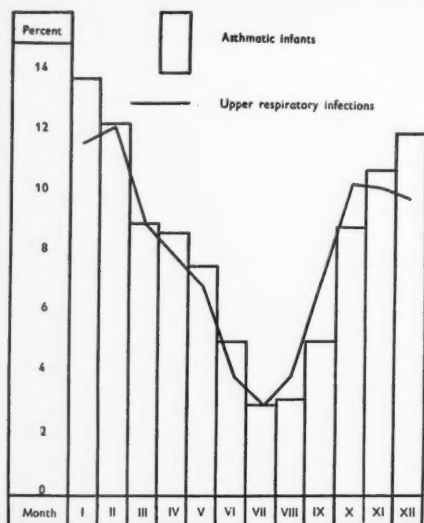


Fig. 3. Monthly occurrence of the onset of asthmatic symptoms in 492 infants and of upper respiratory infections in Malmö in 1951, 1954 and 1958. Total number of cases = 24,972.

in the white blood cell count (above 12,000) in 23 per cent.

From Fig. 3 it is seen that the first occurrence of the asthmatic symptoms in these infants has a distinct seasonal curve, which follows closely the seasonal curve of upper respiratory infections in Malmö.

From Fig. 4 it is seen that the asthmatic infants exhibit a certain tendency to overweight, even if the majority lies within normal limits.

Discussion

The figure obtained here for the occurrence of asthmatic ailments in the first year of life is strikingly high compared with figures from other sources (Bray 22 %, Winge Flensburg 15 %). This indicates that the criteria for the diagnosis of asthma in infancy vary in different places,

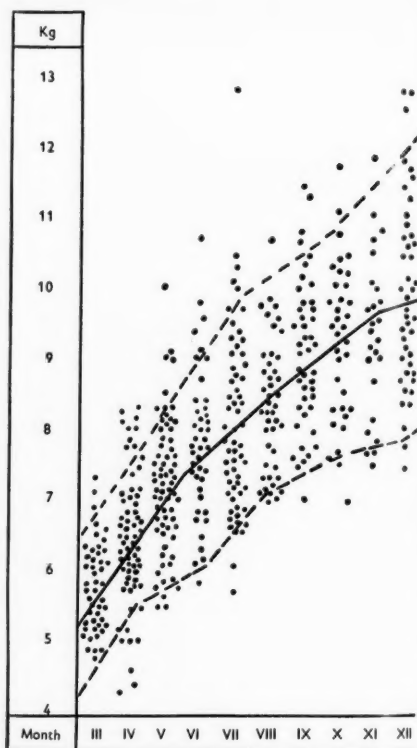


Fig. 4. Weight of 468 infants with asthmatic symptoms. Fulldrawn line = average weight of normal children. Broken lines = normal variations (von Sydow).

but it can also be due to the fact that the cases are not always satisfactorily assembled. If one makes retrospective examinations of cases with genuine asthma, as has often been done, one loses all the cases who have become freed from their asthmatic symptoms and thus obtains too high an average age for the onset of the disease. In order that a prognostic investigation of asthmatic children may have some value, one must thus begin with the first onset of asthmatic symptoms. As is seen from this investigation 80 per cent of all the

children who had asthmatic symptoms during the first year of life have become symptom-free before the age of 6 to 11 years.

The present findings (Table 1) indicate that there is no fundamental difference between so-called genuine asthma and bronchitis asthmatoïdes, a conclusion which has also been drawn by Winge Flensburg.

The asthmatic symptoms in infancy occur, as is seen from the investigation, almost only in connection with an infection, which—even if this is not apparent from the foregoing—is localized to the upper respiratory tract. In addition to this infection certain factors contribute to the occurrence of the asthmatic symptoms: i.e., disposition to allergic diseases, evidently some cellular or possibly hormonal factor since boys are particularly affected, and a constitutional factor since a certain tendency to overweight also exists.

The fact that the asthmatic symptoms occur primarily in infants is more difficult to understand. It cannot be dependent on infection as such, since children in the age of 1 to 3 years are affected considerably more often by upper respiratory infections than infants but in spite of this exhibit asthmatic symptoms much less frequently. One must assume that (1) anatomic conditions play a role, i.e., the narrow bronchi of the infant predispose to the occurrence of the syndrome or (2) the earliest occurring

catarrhal infections initiate antigen-antibody reactions, which the organism soon learns to resist.

Summary

Of 1092 children with asthmatic symptoms, who were treated during the period of 1949 to 1958 at the Flensburg Children's Hospital, 47 per cent had developed their first symptoms during the age of 0 to 1 year. In 87 per cent the symptoms had appeared before 5 years of age.

Boys comprised 63 per cent of the cases. From 7 years of age the risk of becoming ill for girls is equally great as for boys.

Eighty per cent of those who had had asthmatic symptoms in infancy were symptom-free at the age of 6 to 11 years.

An acute infection can be demonstrated in the majority of infants with asthmatic symptoms.

The season of the first occurrence of the asthmatic symptoms coincides with that of acute upper respiratory infections.

Children who have had asthmatic symptoms in infancy and at the time of the investigation were in the age of 6 to 11 years form a group between children of the same age with genuine bronchial asthma and a control group in regard to heredity to asthma and eczema and the risk of developing eczema and hay fever. They have also an increased risk of developing genuine bronchial asthma but not of developing upper respiratory infections.

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CASE REPORT

A Case of Idiopathic Auto-Immune Haemolytic Anaemia due to Anti-e

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Although the mechanism of auto-immunization is not understood, the researches of the past decades have rendered possible means of elucidating those forms of the phenomenon that result in haemolytic anaemia. The successive advances in serology and improved techniques of estimating the life span of the red blood cells constitute the most important keys to this development (cf. Dacie (3), Mollison (14)). One result of the advances in clinical isotope research, embracing improved means of assessing the degree of destruction of erythrocytes in different organs, has been the more exact establishment of the indications for splenectomy in these cases (Hughes Jones & Szur (7)).

The value of these techniques in the diagnosis and treatment of haemolytic anaemias is illustrated by the case now described.

Methods

Routine haematological investigations were carried out by standard techniques.

The osmotic resistance of the red cells was determined by Ponder's method, as modified by Sjölin (15).

The mechanical resistance of the red cells was measured by the method of Shen, Castle & Fleming, as modified by Sjölin (15).

The haemoglobin was analyzed by zone electrophoresis at pH 8.6 and ionic strength 0.05, employing potato starch as supporting medium, as described by Kunkel, Ceppellini, Müller-Eberhard & Wolf (9).

The haptoglobin concentration was determined by the technique of Laurell & Nyman (10).

The red-cell survival and blood volume were measured with Cr⁵¹-labelled red cells in accordance with the principle of Gray & Sterling (6). In our series of 12 auto-transfusions in 12 healthy male adults the mean apparent half-life was 27.5 days (SD = ± 2.25 days).

Surface counting over the heart, spleen, and liver was carried out as described by Hughes Jones & Szur (7).

The serum bilirubin concentration was determined by the method of Malloy & Evelyn (12), modified for 0.2 ml of serum.

'L.E.' cell phenomenon was searched for by the method of Snapper & Nathan (16).

The serological investigations were performed by standard methods. Elution of antibodies from the patient's erythrocytes was carried out by Weiner's method as described by Mollison (13). Both the eluate and the patient's serum were examined by

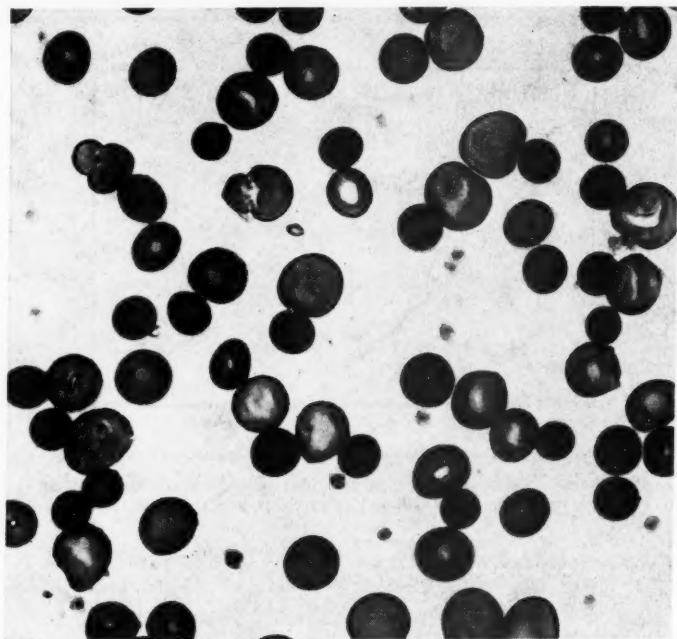


Fig. 1. Photomicrograph of blood smears before splenectomy.

use of albumin-suspended, and enzyme-treated (trypsin and papain) red cells and by the antiglobulin test (Coombs's test).

Case Report

The patient was a boy born on September 5th, 1945. The father suffered from pulmonary tuberculosis. The mother died in 1958 of ovarian carcinoma. Two brothers and one sister are alive and well. The maternal grandmother and a maternal uncle died of gastric carcinoma. There were no known cases of blood disease in the family.

During the first year of life the patient had eczema, but since then has not shown any allergic manifestations. In 1951 he was treated as an in-patient at the Department of Child Psychiatry for behaviour disorder. The boy was and still is slightly mentally retarded, stubborn, and uncommunicative, with periodic outbursts of temper. In August

1949 he started to complain of substernal pain, sometimes radiating out to the left side. In October 1956 he was therefore examined at the Paediatric Out-Patient Department of the University Hospital, Uppsala. The pains were thought to be functional. The chest X-ray and electrocardiogram were normal, the blood pressure was 115/75, and the haemoglobin 13.4 g/100 ml.

At the beginning of June 1958 the boy's father noticed that the child was very pale, and seemed tired. The patient was admitted to the Paediatric Department of the University Hospital on June 16th 1958. Up to this time as far as is known he had received no blood either intramuscularly or intravenously.

Clinical examination showed the physical development to be normal. He was very pale, with slight lemon yellow tinging of the skin and conjunctivae. The liver and spleen were not palpable, and the lymph nodes not enlarged.

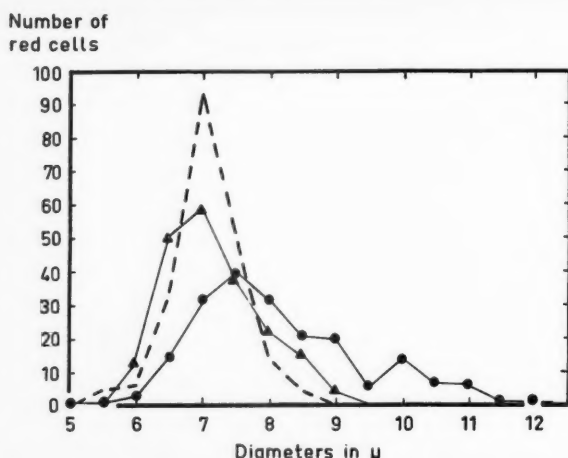


Fig. 2. Red-cell-diameter distribution curves prepared from dried films of peripheral blood before (●—●) and after splenectomy (▲—▲). The dotted line indicates the mean normal curve.

Haematological investigation revealed anaemia (Hb 5.3 g/100 ml), reticulocytosis (27.2%), marked aniso- and poikilocytosis, numerous spherocytes (Figs. 1 and 2), polychromasia, and a few Howell-Jolly bodies. The mean red-cell diameter was 8.1 μ , mean cell volume 106 cu μ , mean corpuscular haemoglobin 33 μ g, and mean corpuscular haemoglobin concentration 31%. The total blood volume was 2497 ml (74.0 ml/kg), and the total red-cell volume 408 ml (12.1 ml/kg). The serum iron was 115 μ g/100 ml and the total iron-binding capacity 260 μ g/100 ml. The osmotic resistance of the red cells was slightly reduced. After incubation at 37°C for 24 hours, the red cells showed a great fall in osmotic resistance (Fig. 3). The red cells also showed diminished mechanical resistance, with 17.8% haemolysis (normal maximum 3%). Starch electrophoresis showed normal proportions of haemoglobin A and A₂. No haptoglobin was demonstrable in the serum. The serum bilirubin was 3.2 mg/100 ml, and the direct van den Bergh reaction was negative. Urobilin was demonstrated in the urine. The leukocyte count was 11,200/cumm with 1680 eosinophils. The thrombocyte count was 431,000/cumm. The serum alkaline phosphatase was normal. The results

of the thymol turbidity test and cephalin-cholesterol flocculation test were normal. X-ray examination revealed slight enlarge-

Haemolysis

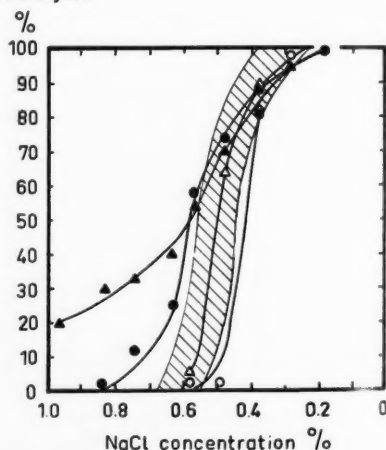


Fig. 3. Degrees of haemolysis in various concentrations of sodium chloride. Red cells from the patient before (●—●) and after incubation at 37°C (▲—▲). Red cells from a healthy adult before (○—○) and after incubation at 37°C (△—△). The hatched area represents the normal variation (± 2 SD) in healthy adults (unincubated red cells).

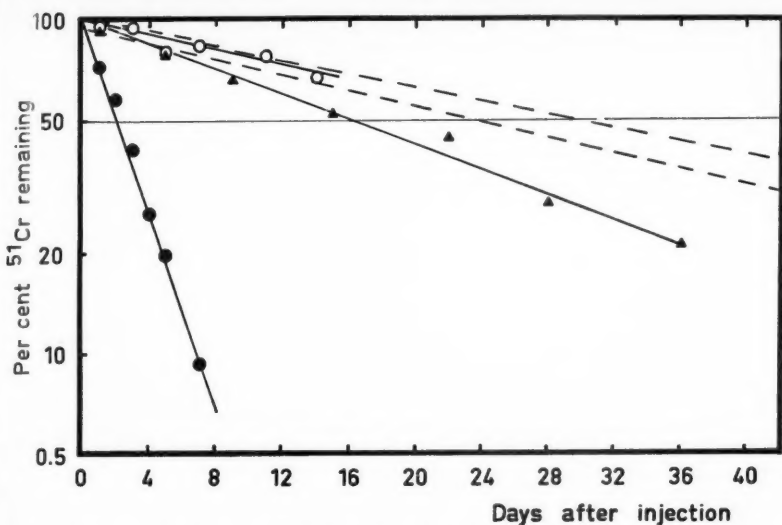


Fig. 4. Survival curves of Cr^{51} -labelled red cells from the patient before (●—●) and after splenectomy (▲—▲). Survival of Cr^{51} -labelled red cells from a healthy adult (type Rh_2Rh_2) after transfusion to the patient and before splenectomy (○—○). The dotted lines indicate the normal variation (± 2 SD) after autotransfusion of Cr^{51} -labelled red cells in 12 male adults.

ment of the spleen (length c. 12 cm). X-ray of the chest, skull, and extremities showed no abnormalities. The erythrocyte sedimentation rate was normal. The faeces contained no occult blood.

The bone marrow (Bo Vahlquist) was hyperplastic. The red blood cells showed marked anisocytosis, with many large cells (? reticulocytes) but also a fair number of microspherocytes. Erythropoiesis predominated, and the appearance was polymorphous, with numerous mitoses and shift to the left to the proerythroblast stage. There was marked reticulum-cell proliferation. Myelopoiesis was sparse, with no special characteristics other than a slight increase in the number of eosinophils.

Serological investigations. The blood group was A,B, Rh +, type CDe (Rh_1). Further Rh typing was not possible because the direct antiglobulin test was strongly positive and because there was no saline-agglutinating antigen available. In addition to cold agglutinin of low titre (1:8) incomplete antibodies

of the warm type were present in the patient's serum, reacting with all types of red cells in a standard panel. The reactions were noted in the antiglobulin test as well as with the albumin and enzyme methods. Using serial dilutions of antiglobulin serum, the direct antiglobulin test was positive in a final dilution of 1:4096, and showed a marked prozone phenomenon. The antibodies on the red cells could be eluted, and they reacted in the same manner as the serum antibodies. After absorption of the eluate with papainized red cells of type O CCDee (Rh_1Rh_1) no antibodies could be detected in the eluate. After absorption with O ccDEE (Rh_2Rh_2) red cells, positive reactions still took place with all types of cells except those of type ccDEE lacking the e antigen. This indicated the presence of both non-specific antibodies and group-specific antibodies of anti-e (anti-hr'') type.

Investigations concerning the survival and destruction of the red cells. Autotransfusion of 2 ml of Cr^{51} -labelled red cells (35 μC) (2 μg

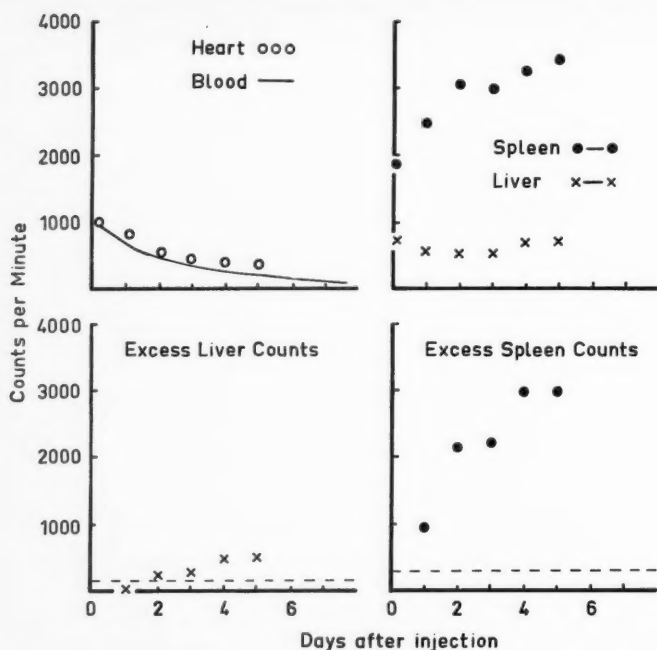


Fig. 5. Results of surface counting over the heart, liver, and spleen following injection of the patient's own Cr^{51} -labelled red cells. The dotted lines indicate the maximum excess counts in normal adults according to Hughes Jones & Szur (7).

Cr/ml) showed an apparent half-life of about 2 days (Fig. 4) (mean cell life = 9 days). (There was no concomitant blood-loss.) Measurement of radio-activity over the heart, liver, and spleen revealed slightly increased accumulation over the liver and greatly increased accumulation over the spleen (Fig. 5). The liver/spleen ratio was very greatly increased (about 5–6 times after the first day).

Course and Treatment

The main haematological data and details of treatment are given in Fig. 6. Since an auto-immune anaemia was undoubtedly present, treatment with 100 mg of prednisone ('Meticorten', Schering) daily was started on 25th June 1958. The dose was reduced successively, and treatment was discontinued after 50 days. Slow improve-

ment in the haemoglobin level was noted during the first 25 days of treatment, and a maximum of 9.9 g/100 ml was reached. The reticulocyte count, which before the commencement of treatment had risen to about 50%, fell during the course of treatment to about 30%. At the same time the serum bilirubin fell to 0.5 mg/100 ml. A side-effect of treatment was rounding of the face. After the dose of prednisone had been reduced to 40 mg per day the haemoglobin concentration was found to be falling, the reticulocyte count and serum bilirubin increasing. At the time prednisone was withdrawn the haemoglobin had fallen to about 4 g/100 ml. The condition of the patient was then poor. He had been pyrexial for 10 days, was fatigued, and had a pulse rate of 130–140 per minute.

New auto-transfusion of 2.5 ml of Cr^{51} -labelled red cells (35 μC) (1.8 μg Cr/ml) again

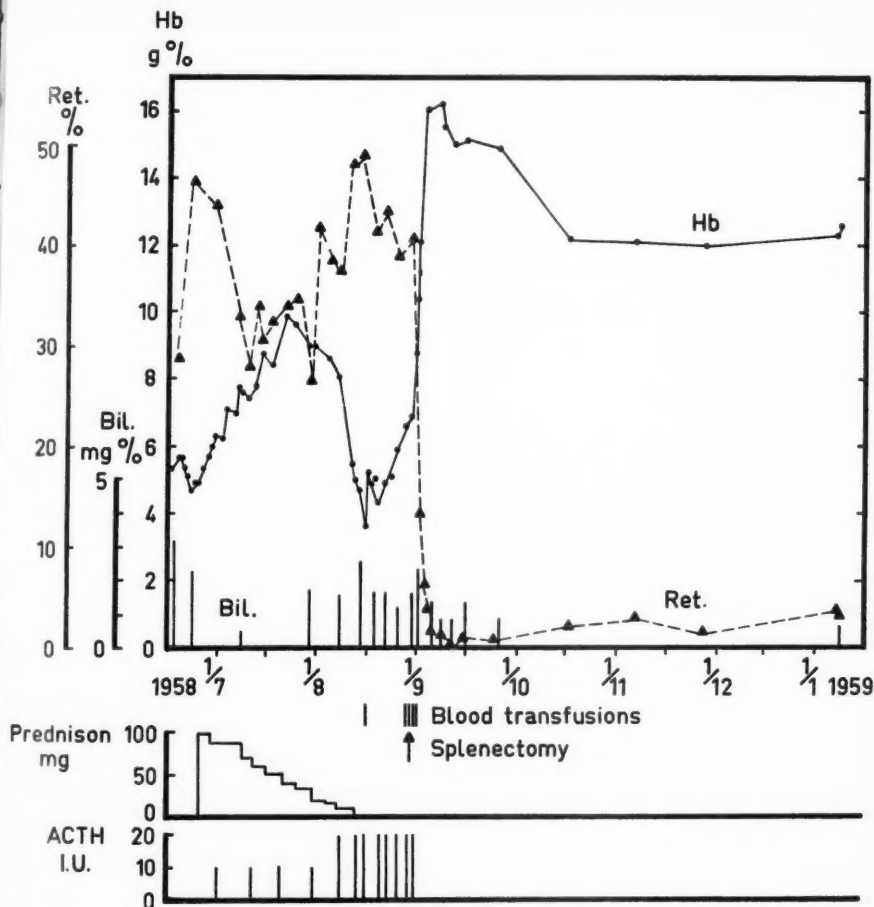


Fig. 6. Significant haematological data and treatment.

showed an apparent half-life of 2 days. Surface counting revealed the same state of affairs as before. In an attempt to determine whether it was the anti-e or the generally-active antibodies that were responsible for the haemolytic process, homotransfusion was carried out with 7 ml of Cr^{51} -labelled red cells ($51 \mu\text{C}$) ($1.0 \mu\text{g Cr/ml}$) of type B ccDEE (Rh_2Rh_2) from a healthy adult donor. These red cells were found to survive for a normal period (Fig. 4). Owing to the poor condition of the patient, 400 ml of

sedimented blood from the same donor had been transfused immediately before the injection of the tagged red cells.

Six days after the transfusion, serological tests showed the presence of anti-e, and also nonspecific antibodies active against 8 different samples of papainized red cells lacking the antigen e (ccDEE).

Since prednisone was not completely effective, even in high dosage, and side-effects occurred, and because it had been demonstrated that destruction of the ery-

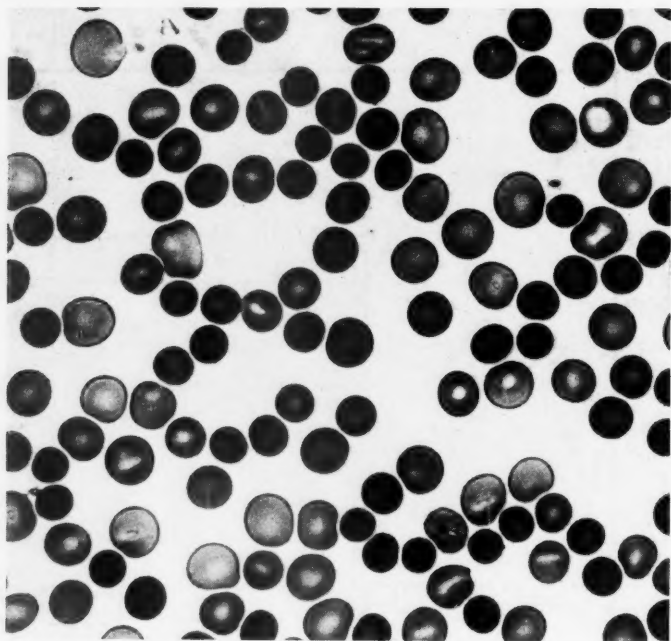


Fig. 7. Photomicrograph of blood smears 4 months after splenectomy.

thromocytes was taking place largely in the spleen, splenectomy was performed on September 1st 1958. At the time of operation the patient received in all 1800 ml of sedimented blood of type O ccDEE¹. ACTH ('Acton Prolongatum', Pharmacia) was given in 8 doses of 20 units during the course of 3 weeks, in the hope of stimulating adrenal function. The spleen weighed about 250 g, and was fairly firm, with a bright red cut surface. Histological examination (G. Hultquist) showed the pulp to be highly vascular, with wide, very prominent sinusoids and fairly large numbers of haemosiderin-containing cells, but otherwise there were no special features. Biopsy of the liver, carried out at the same time, revealed a normal histological picture. The patient stood up well to the operation, and the subsequent course was free from complications. The effect of the procedure upon the haemo-

globin, reticulocyte count, and serum bilirubin is evident from Fig. 6. The boy was discharged from Hospital on September 17th 1958, his general condition and physical capacity rapidly improved, and since September 29th he has been able to cope with school work, play, and sports equally as well as other children in his class.

The boy was re-admitted to the Pædiatric Department of the University Hospital, Uppsala for the period 7th-8th January 1959, for *follow-up examination*. Since the red blood cells of type ccDEE transfused at the time of operation could by now be considered to have been eliminated, it was possible more accurately to assess the result of operation. The haemoglobin concentration was normal (12.5 g/100 ml), as was also the

¹ This blood was kindly supplied by Dr. B. Gullbring, Stockholm, and Dr. L. Ryttinger, Gothenburg.

serum bilirubin (0.4 mg/100 ml) (Fig. 6). There was moderate reticulocytosis (3-4%). There were still obvious aniso- and poikilocytosis, numerous spherocytes (Figs. 2 and 7), and a few Howell-Jolly bodies. The mean red-cell diameter was $7.2\ \mu$, the mean corpuscular volume $100\ \text{cu}\mu$, the mean corpuscular haemoglobin $34\ \mu\text{g}$, and the mean corpuscular haemoglobin concentration 34%. The total blood volume was 2710 ml (76.7 ml/kg), and the total red-cell volume 838 ml (23.7 ml/kg). The osmotic resistance of the red cells was normal, the mechanical resistance slightly reduced (5.8% haemolysis compared with a maximum of 3% normally). The serum haptoglobin content was 15 mg/100 ml (a low value, but not indicative of a marked haemolytic process).

The patient's red cells were agglutinated by the antiglobulin serum previously used, in a titre of 1:2048. They were thus about as strongly sensitized as before the operation. The eluate from the patient's red cells showed the presence of the same types of antibodies as before, the anti-e possibly being somewhat stronger than the non-specific antibody. The circulating antibodies of the serum were no longer demonstrable by the albumin method, but otherwise the reactions were about the same as before operation. After auto-transfusion of 2.0 ml of Cr^{51} -labelled red blood cells ($12\ \mu\text{C}$) ($0.6\ \mu\text{g}\ \text{Cr/ml}$), the apparent half-life was 16 days (Fig. 4) (mean cell life = 47 days). There was no blood-loss at this time. The thrombocyte count was 659,000/cumm, and the eosinophil count 48/cumm. No 'L.E.'-cells were demonstrable on any of 4 occasions after splenectomy. Since June 1958 the boy has not complained of substernal pain.

Discussion

The case of acquired auto-immune haemolytic anaemia described was of the idiopathic type. The life-span of the red cells was greatly reduced (mean cell life 9 days). Antibodies were demonstrable, but the reason for the auto-immunization

is completely obscure. No infective illness or other condition that might have started the haemolytic process is known to have occurred, and no drugs had been administered immediately before the commencement of the illness. The part which the child's allergic diathesis, manifested as infantile eczema and as eosinophilia during the initial stage of the haemolytic illness, may have played in bringing about the autoimmunization cannot be determined.

The serological investigations revealed warm auto-antibodies, both "nonspecific" and anti-e.

Antibodies of the non-specific type are those most commonly found in acquired haemolytic anaemia such as this, but in addition blood-group-specific antibodies, usually within the Rh system are sometimes found, as in this particular case. Rare cases have been described in which blood-group-specific antibodies alone were present (Ley, Mayer & Harris (11); Dacie (3); Mollison (14)). When several types of antibodies are present together it is as a rule impossible with the aid solely of serological findings to establish which of them is mainly active. Since red cells not possessing e-antigen (type ccDEE) showed normal survival after transfusion to the patient, it may be regarded as established that it was the anti-e antibody that was mainly responsible for the haemolytic disease. As the tests with Cr^{51} -labelled red cells were not carried out under entirely unequivocal conditions, the patient having received a transfusion of 400 ml of blood immediately before the investigation on ccDEE red cells, it is still theoretically possible that the nonspecific antibodies contributed to the severe haemolysis. In that case the transfused red cells might

have absorbed a sufficiently number of the nonspecific antibodies to show a normal red cell survival time. However, six days after the transfusion, nonspecific antibodies were demonstrated in the patient's serum. It is therefore highly improbable that the nonspecific antibodies could have played a major part in bringing about the increased destruction of the patient's red cells.

After auto-transfusion of the patient's own Cr⁵¹-labelled red cells, there was a considerable excess of radio-activity over the spleen, indicating that the red cells were being destroyed mainly in that organ (cf. Hughes Jones & Szur (7)). These observations tally with the view that red blood cells coated with incomplete Rh antibodies are largely destroyed in the spleen (Jandl, Jones & Castle (8); Cutbush & Mollison (2)).

The effect of corticosteroids in acquired haemolytic anaemia varies, and cannot be predicted. Since it is commonly good, however, it is now the rule to commence the treatment of haemolytic anaemias by giving a course of steroids (Dameshek & Komminos (4); Chertkow & Dacie (1)). In this case the effect was incomplete, however, despite 50 days' treatment with a dose so high that a sideeffect in the form of 'moon' face developed. Because of this, and because erythrocyte destruction had been shown to be taking place mainly in the spleen, splenectomy was carried out. This was followed by clinical and haematological improvement. As the immediate improvement might have been due entirely or in part to the large blood transfusions that were given at the time of operation, the boy was re-examined 4 months later, when the foreign red cells could be assumed to have been eliminated. The patient's

own Cr⁵¹-labelled red cells then showed moderately shortened survival (mean cell life about 47 days), which would explain the secondary signs of haemolysis (slight reticulocytosis, increased excretion of urobilin in the faeces, and slightly diminished serum haptoglobin concentration). It is probable that abnormal destruction of red cells was still taking place in the liver: before splenectomy a slightly increased accumulation of Cr⁵¹ had been demonstrated in this organ.

Thus splenectomy did not lead to complete cure, but brought about a diminution in the break-down of erythrocytes so great that the new formation of red cells balanced the destruction.

Two theories may be put forward to explain the reduced breakdown of red cells. Firstly, it is possible that the removal of the spleen involved also the removal of an important source of antibodies. This view is contradicted by the persistent serological reactions. Secondly, and more probably, the reduced destruction of erythrocytes may have been due to the elimination of the passive filtering action of the spleen, as a result of which red cells coated with incomplete antibodies are rapidly sequestered (cf. Jandl, Jones & Castle (8)).

It is, of course, too early to express any views on the long-term outlook in this case. It is possible that steroid therapy may be necessary in the future.

Summary

The case is described of a 13-year-old boy with auto-immune haemolytic anaemia, in which the blood-group-specific

antibody anti-e was probably responsible for the haemolytic process. Survival studies on Cr⁵¹-labelled red cells were carried out

before and after splenectomy. The operation was followed by clinical and haematological improvement.

Cas d'anémie hémolytique idiopathique auto-immune due à anti-e

Description du cas d'un garçon de treize ans atteint d'anémie hémolytique auto-immune, chez lequel l'anti-corps anti-e spécifique du groupe sanguin était responsable du processus hémolytique. Des études de survivance sur des cellules rouges marquées de Cr⁵¹ furent faites avant et après la splénectomie. L'opération fut suivie d'une amélioration clinique et hématologique.

Ein Fall von idiopathischer autoimmuner hämolytischer Anämie auf Grund von Anti-e

Es wird der Fall eines 13jährigen Jungen beschrieben, der an einer autoimmunen hämolytischen Anämie litt, bei welcher der blutgruppenspezifische Antikörper Anti-e für den hämo-

lytischen Prozeß verantwortlich war. Vor und nach der Splenektomie wurden Kontrolluntersuchungen mit Hilfe von mit Cr⁵¹ markierten Erythrozyten durchgeführt. Der Operation folgte eine klinische und hämatologische Besserung.

Un caso de anemia hemolítica autoinmune e idiopática debida a anti-e

Se describe el caso de un muchacho de 13 años con anemia hemolítica autoinmune en el que el anticuerpo anti-e, específico del grupo sanguíneo, era responsable del proceso hemolítico. Se realizaron estudios de control a base de eritrocitos marcados con Cr⁵¹ antes y después de la esplenectomía. La operación fue seguida por una mejora clínica y hematológica.

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CASE REPORT

Lactosuria and Amino-Aciduria in Infancy

A New Inborn Error of Metabolism?

by SVEN DARLING, OLE MORTENSEN and GUNNAR SØNDERGAARD

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Lactose is excreted only in very small amounts in the human urine (6). In non-pregnant women and in men, Flynn *et al.* (10) found that lactose was present in 8–9 % of the subjects studied, but only in very small amounts demonstrated by paper chromatography. In the urine of pregnant women it is found in moderate quantities (usually < 100 mg %), and it can be recovered from the urine of all puerperal women about the fourth day after delivery (10, 24); in these cases the lactose has been produced by the lactiferous glands.

Lactose (usually < 100 mg %) was found in 28 % of full-term newborn infants (13). In premature infants it was present in 65 %, but also here only in very low concentrations revealed by paper chromatography (14).

About the opening of this century, German authors (12, 19) reported to have found lactosuria in children with chronic dyspepsia.

In studies of the urine of 1000 children,

Bickel (1) found 13 cases of "secondary" lactosuria, including two with hiatal hernia.

Durand (8, 9) mentioned a 13-month-old child with considerable lactosuria (up to 1.8 %) and renal acidosis. The parents were related, and a sibling had died from congenital anomalies. The child suffered from refractory dyspepsia, was underweight and died at the age of 15 months. Durand described the disease as idiopathic lactosuria.

Apart from these, no other cases of excessive urinary excretion of lactose seem to have been reported in the paediatric literature—"lactosuria is not a problem in the pediatric age period" (Wolman).

That ingested lactose is rarely excreted in great amounts in the urine is due to the fact that it is completely split up into glucose and galactose by the action of beta-galactosidase. This splitting occurs exclusively in the small intestine, partly on the surface of the glandular cells and partly in the lumen of the intestine (Heilskov (15)). If the lactose is not split

¹ Read at a Staff Meeting of Aarhus Kommunehospital on Dec. 3, 1957.

up, it may be absorbed, but will then rapidly be excreted in the urine.

Two fatal cases of severe alimentary lactosuria and amino-aciduria are reported below, and two other cases in which the infants apparently died from the same disease are mentioned.

Methods of Investigation

Osazone determination and paper chromatography were used for the identification of lactose. In the chromatographic analyses Whatman paper No. 1 was used in both cases. In Case 1, ethylacetate-pyridine-water, 4:2:1, v/v, was used as the solvent and aniline phosphate as the spraying reagent (Bryson & Mitchell (2)). The samples were hydrolysed with $\frac{1}{3}$ N HCl on water bath for 20 minutes. An amount of 5 μ l of 1% lactose solution in water was used for comparison. In Case 2, the solvent was butanol-pyridine-water, 10:5:7, v/v (Jeanes *et al.* (18)) and the spraying reagent aniline phthalate (Partridge (22)).

In Case 2, Hagedorn & Jensen's tablet method supplemented by glucose oxidase (Søndergaard (23)) was used for the quantitative determinations of glucose and other reducing substances in blood and urine. After haemolysis of 0.1 ml blood in 1 ml water, 0.2 ml glucose oxidase solution was added. This solution had been prepared by dissolving 5 mg glucose oxidase (Notatin Leo) in 5 ml acetate buffer, pH 5.6. After incubation for 90 minutes at 37°C., precipitation and titration by Hagedorn & Jensen's technique were performed.

Identification of Amino Acids

Two-dimensional chromatography on Whatman paper No. 1 as described by Consden & Gordon (3, 4) and Dent (7) was used for the detection and identification of amino acids. The chromatograms were developed with pyridine-butanol-water, 1:1:1, v/v (Morrison (20)) followed by phenol-

water, 75:25, w/v, in an ammonia atmosphere. After drying, the chromatograms were sprayed with a 0.2% (w/v) solution of ninhydrin in acetone.

Case Reports

Case 1.—A 3-week-old boy (K.L.) was admitted to the University Clinic of Paediatrics, Aarhus, on May 5, 1957.

Family history.—A paternal uncle of the father had had diabetes mellitus in later life. The father's sister had lost a baby aged 2 weeks. The parents were unrelated, but came from the same district (see pedigree chart, Fig. 5).

The father was 31 years old and in good health. The mother was 26 years of age. She had pronounced exophthalmos, but no other manifestations of hyperthyroidism. Following normal pregnancies, she had given birth to three children. (For further details as to the first two children, see below.)

The boy weighed 4400 g at birth; length 56 cm; asphyxia and neonatal jaundice were absent. He was breast-fed at first, but after 10 days a supplementary milk formula had to be given. On the seventh day of life the infant began to vomit. The vomiting gradually increased in volume and frequency, and the infant became flabby and lost weight.

During the hospital stay occasional vomiting occurred, and the number of motions varied from a few to about ten in 24 hours. The body weight was constantly decreasing; at the age of 6 weeks it was 1200 g below the birth weight. Convulsions did not occur.

For successive periods, the patient was given a 50% milk formula, breast milk and milk-free feeds. Occasionally, pure galactose was added to the diet. Parenteral fluid (glucose water, Darrow's fluid) was administered.

The clinical condition was independent of the diet, but owing to the poor general condition one particular diet was given only for a few days in succession, since none of the dietary regimens improved the condition.

Clinical examination did not reveal jaun-

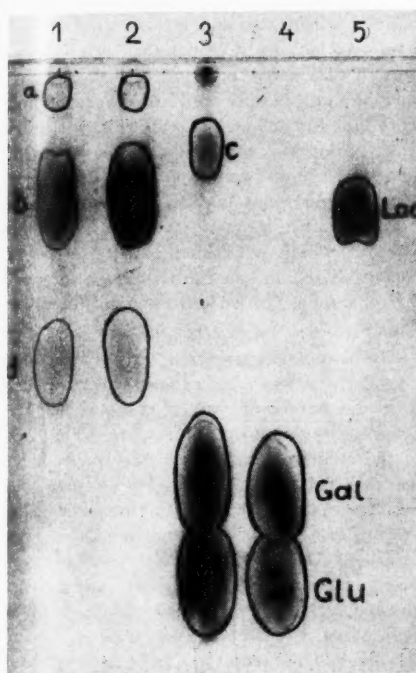


Fig. 1. One-dimensional chromatograms of (1) urine, 5 μ l, (2) urine + 10% lactose, 5 μ l of each, and (3) hydrolysed urine, 5 μ l.

Solvent ethylacetate-pyridine-water, 4:2:1, v/v. Spraying reagent aniline-phosphate. Spot b corresponds to lactose, while the spots, a, d and e are unidentified.

dice or cyanosis. The patient was critically ill, emaciated and, for periods, dehydrated. Skin rash or enlargement of the lymph nodes, spleen or liver did not occur. Auscultation of the lungs and heart showed normal conditions. The muscular tone and deep reflexes were normal.

Ophthalmological examination did not reveal any abnormalities; specifically, the refractive media were clear.

At first, the boy took his feedings fairly well but later he had to be fed by gavage. The body temperature was sometimes slightly elevated. Slow deterioration occurred, independent of diet and treatment, and the patient died at the age of 6 weeks.

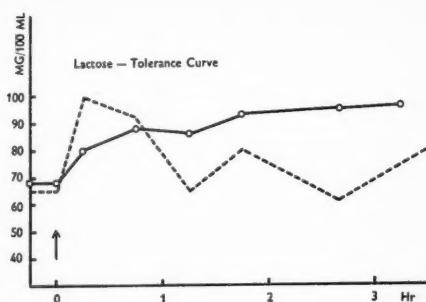


Fig. 2. Total reduction in blood. Lactose, 7 g, was fed at zero time to Case 1 (O—O) and to a normal infant of the same weight (---).

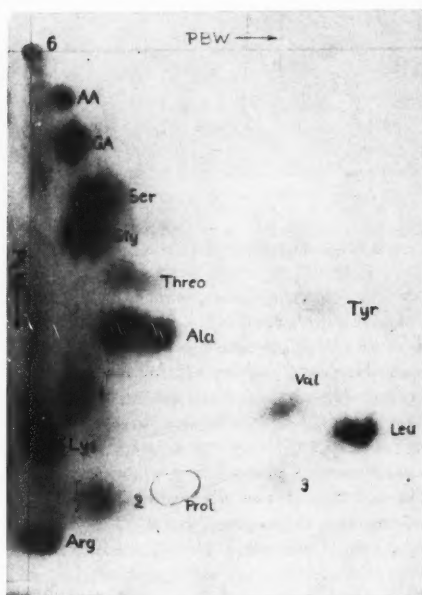


Fig. 3. Two-dimensional chromatogram of 25 μ l of urine collected in a period with urinary excretion of lactose.

PBW, solvent pyridine-butanol-water, 1:1:1, v/v.

PhW, solvent phenol-water, 75:25, w/v.

Key to abbreviations: AA, aspartic acid; GA, glutamic acid; Gly, glycine; Ala, alanine; Val, valine; Leu, leucine and/or isoleucine; Ser, serine; Threo, threonine; Prol, proline; Tyr, tyrosine; Lys, lysine; Arg, arginine; Tau, taurine; 1, 2 and 3, unidentified compounds.

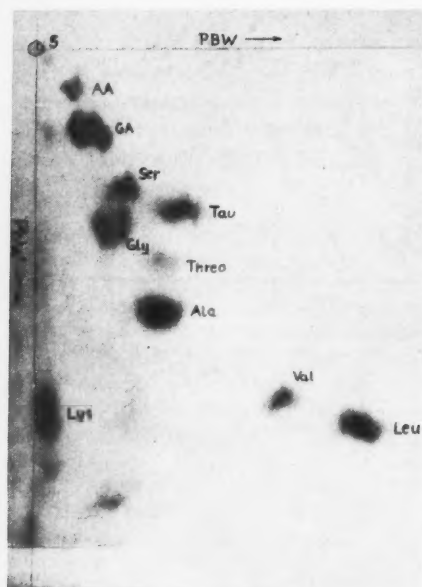


Fig. 4. Two-dimensional chromatogram of 25 μ l of urine collected in a period without urinary excretion of lactose. For details, see text of Fig. 3.

Laboratory examinations.—The urine reduced Fehling's solution, and osazone determinations and paper chromatography revealed that the reducing substance was lactose (Fig. 1). It was present in a concentration of 1–1.5%.

Lactose was present only when the patient was given milk and disappeared completely when he was on a milk-free diet. Fasting blood sugar was normal; while a milk formula was given, it was 130 mg % on one occasion. Galactose-tolerance tests (total reduction) were normal with a maximum increase of 30 mg %.

The result of a lactose-tolerance test (7 g lactose in 40 ml water given by mouth after fasting for 15 hours) appears from Fig. 2. Samples of urine collected 75 and 160 minutes after the administration of lactose were examined for sugar by paper chromatography; considerable amounts of lactose (> 1%) were present in both samples. Blood

samples withdrawn at the same time showed a trace of lactose. Following the administration of the same amount of lactose in a normal child, lactose could not be recovered from blood or urine.—In addition, the urine was studied repeatedly during a period of 48 hours; lactose was present but disappeared after fasting for a few hours. Amino acids were present in large amounts (Fig. 3) in the samples which contained lactose, whereas decreased amounts of amino acids were found in the samples which did not contain sugar (Fig. 4).

The urine was negative for protein, and Legal's test was also negative. The spinal fluid did not reveal any increase in cells or protein; it was not studied for sugar. Cultures of the stools did not reveal any pathogenic bacteria. The faeces showed no proteolytic activity. Anaemia was absent. Electrocardiography showed normal conditions.

Autopsy did not reveal any essential macroscopic changes. Histological examination showed that some fatty degeneration was present in the central parts of the acini of the liver. The structure of the kidneys was normal; the glomeruli were a little plump. The epithelium of the convoluted tubules was swollen; the cells were very bright with vacuolated cytoplasm, but the nuclei were well preserved. Staining by the periodic-acid-Schiff (PAS) method showed that the cells were filled with PAS-positive granules, and the lumina of the straight tubules were filled with a homogeneous PAS-positive material. Sudan staining did not reveal fat in the parenchymal cells. The pancreas had relatively many and large islets of Langerhans of normal type. No signs of cystic fibrosis of the pancreas were observed. The adrenals were normal (Dr. Tage Lund).

It may be of interest to make brief mention of the two siblings of the patient, of whom we have obtained information from other hospitals.

A brother (J.L.) of the patient died at the age of 4 weeks in 1954. The birth weight was 3500 g. The symptoms were vomiting and failure to thrive. At death, the boy weighed 1 kg less than at birth.

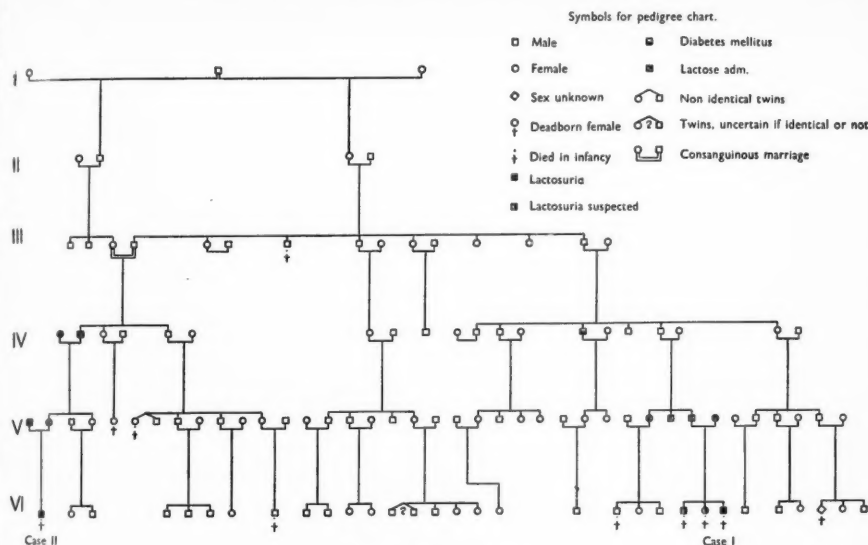


Fig. 5. Pedigree chart.

He was breast-fed at first and later given carrot powder in water, which resulted in a considerable improvement in the condition. He was then given a milk formula.

On the next day he suddenly became cyanotic and pale with a slow pulse. Later clonic convulsions developed, and death ensued within a few hours. The urine contained protein and sugar, but the sugar was not identified. Blood Group O, Rh-positive. Histological examination of the kidneys showed that the epithelium of the convoluted tubules was rather bright and vacuolated, but PAS-positive granules were not observed. In a few glomeruli and collecting tubes, a considerable amount of a PAS-positive clotted fluid was present (Dr. Tage Lund).

A sister (E.L.) of the two aforementioned boys died at the age of 4 weeks in 1955. The symptoms were vomiting and failure to thrive. The infant was breast-fed at first, but after the onset of vomiting a supplementary milk formula was given. The urine was not studied. Blood Group O, Rh-positive.

Case 2.—A 17-day-old boy (C.L.H.) was admitted to the Department of Internal

Medicine, Aalborg Amtssygehus, in August 1958.

It was later elicited that the boy was related to the three aforementioned siblings (see Fig. 5), whose parents came from the same district.

Family history.—A cousin of the mother (a paternal uncle's daughter) had lost a boy aged 10 days (Fig. 5). A few days after birth jaundice developed, and on the ninth day of life the infant was very flabby, refused its feedings and began to vomit. Cyanosis and respiratory distress occurred, and death ensued on the next day. The urine was not analysed.—Otherwise, there were no particular diseases in any of the near relatives.

The parents of the patient were unrelated. The father was 23 years and the mother 22 years old; both were in good health. The pregnancy had been normal. The mother's blood group was O, Rh-positive. She had not previously been pregnant. The delivery had been normal. The boy weighed 3455 g and was not asphyxiated. Jaundice had not been observed before admission. The infant had been breast-fed at home; he was admit-

ted to hospital because of vomiting which began shortly after birth.

On admission, the boy weighed 3360 g; he was slightly undernourished, but not dehydrated or critically ill. The skin and sclerae were slightly jaundiced. During the next few days the jaundice increased a little, but it disappeared within a fortnight. The liver extended 2 to 3 cm below the costal margin. The spleen was not enlarged. Ophthalmological examination showed normal conditions; specifically, cataract was absent.

A slight rise in temperature was occasionally observed. Owing to hypogalactia, a supplementary milk formula was given. He took his feedings well, but each feeding was followed by slight vomiting, sometimes projectile in character. On the third day in hospital, a marked aggravation of the disease occurred. The patient became flabby and dehydrated, and the vomitus was blood-tinged. Following parenteral fluid administration and cortisone some improvement occurred. Because of suspected galactosaemia the infant was placed on a milk-free diet, first glucose water, then Nutramigen, and later lactose-free feedings prepared by the method of Holzel (16). The general condition fluctuated, with several critical periods during which transient haematemesis and melaena occurred. He was treated with fibrinogen, intravenous infusion of serum, vitamins, potassium and sodium.—During the better periods he took small feeds eagerly, but occasionally had to be fed by gavage. On occasional days vomiting did not occur. Stools were usually normal. Considerable gastric retention developed, and roentgen examination revealed pyloric stenosis, which gradually became very conspicuous. Gastric peristalsis could be observed only relatively late, but eventually it became very violent with peristaltic waves reaching down to the right iliac fossa.

During the poorer periods, the mouth revealed severe thrush, which was treated with silver nitrate and Mycostatin.

Methyl atropine was without convincing effect on the vomiting and had to be aban-

doned because of the development of toxic reactions.

Owing to the poor general condition surgical treatment could not be given. The course continued downhill, and the infant died at the age of 53 days.

Laboratory examinations.—On admission, proteinuria was present, but the urine did not contain glucose (glucose-oxidase paper (clintix)).

Urine collected a few hours after the patient had been put on a milk-free diet had a weak reducing effect (Fehling). The reduction determined by the method of Hagedorn & Jensen corresponded to that of 593 mg% glucose. The reducing capacity remained almost unchanged (563 mg%) after treatment with glucose oxidase. At the same time, the blood showed a residual reduction of 46 mg% after treatment with glucose oxidase. The urinary excretion of sugar had ceased 24 hours later, but returned at once when the patient was again put on a milk formula for one day.

The sugar was identified as lactose by paper chromatography, and the lactosuria was confirmed by osazone determination.

Paper chromatography also revealed a pathological amino-aciduria, most pronounced in lactose-containing samples of urine.

The proteinuria disappeared when the patient had been on a milk-free diet for a few days.

During the milk-free period, the blood-sugar level was normal, apart from a few low fasting values (minimum 55 mg%).

Microscopic examination of the urine showed normal conditions.

ESR 2 mm/hour; Blood Group O, Rh-positive. Anaemia was absent. The white blood cells and the bone marrow showed normal conditions. Blood urea varied from 48 to 84 mg%, serum potassium 10–18 mg%, serum sodium 300–350 mg%, serum chloride 291–362 mg%, serum calcium 10.1 mg%, prothrombin concentration 71%, serum fibrinogen before the administration of fibrinogen 50 mg%. Total protein was 4.0–5.4%, of which paper electrophoresis

showed the following distribution: albumin 60%, alpha-1 globulin 3.4%, alpha-2 globulin 12.4%, beta globulin 7.5%, gamma globulin 16.2%. Thymol turbidity was 1.9-1.5 Maclagan units.

Autopsy revealed that the stomach was markedly dilated with violent hypertrophy of the pyloric musculature. The duodenal mucosa projected into the stomach. The lungs showed scattered atelectases; the remaining organs showed no pathological features.

Histological examination of renal tissue revealed considerable precipitations in the distal tubules and, particularly, in the collecting tubes. Haematoxylin staining gave a bluish-dark colour suggestive of calcium. In some places, the precipitates were surrounded by clusters of epithelial cells, which were occasionally, in turn, surrounded by white blood cells. In several areas, especially in the distal tubules, there were crystalline precipitates, which were distinctly birefringent in polarised light. The interstitial tissue was somewhat hyperaemic. Scattered, but marked accumulations of PAS-positive, clotted fluid were seen in the glomeruli and collecting tubes.

The liver showed extramedullary haematopoiesis, and bile pigment was occasionally present in the hepatic cells. The stomach showed pronounced muscular hypertrophy in the pyloric region. The spleen, heart, pancreas and adrenals showed no pathological features (Dr. Harald Olesen).

In relation to the examination of this patient, lactose was given to eight close relatives of the four children (Fig. 5). They were given 50 g lactose by mouth on an empty stomach. Samples of the urine were collected before, and 2, 4 and about 8 hours after the intake of lactose. The urine was studied by the aforementioned chromatographic technique, but none of the samples revealed lactose.

Discussion

The course of the disease and the considerable alimentary lactosuria and amino-

aciduria in the two infants (K.L. and C.L.H.) are strongly in favour of the assumption that they suffered from the same disease. It is also reasonable to assume that the two siblings (J.L. and E.L.) of K.L. had died from this disease. The symptoms began at about the same age, and all four infants were only a few weeks old at death. When the mother followed the course in her third child, she was convinced that the boy suffered from the same disease as the first two children; the course and the symptoms were exactly the same in all three infants.

The assumption that the infants suffered from the same illness was supported not only by the resemblance in the clinical course, but also by the fact that sugar was revealed in the urine in three of the cases (in two, identified as lactose).

As mentioned in the opening section of this paper, urinary lactose in the amounts found in the two patients is a rare symptom. Investigations in progress show that lactosuria may occur in healthy infants after oral administration of pure lactose in aqueous solution.

The question as to whether there was any direct relationship between the lactosuria and the pyloric stenosis in Case 2 cannot be answered with certainty. We believe that it must be considered to be a mere coincidence. By a review of 150 case records for children with pyloric stenosis, we found only one case in which a non-identified sugar was revealed in the urine on one occasion, and traces of sugar were revealed in two additional cases. In the remaining 147 children with pyloric stenosis the urine was negative for sugar.

The question is then: From what disease did these infants suffer? In addition to

dyspepsia and failure to thrive, its main feature seemed to be a defective breakdown of lactose, i.e. absence of lactase activity in the intestinal tract. The lactose which does not split up will, at least partially, be absorbed and may be toxic to the organism and be excreted in the urine. What damage the lactose may have caused is unknown, and so are the causes of death. In Case 2, pyloric stenosis may have been a contributory factor in causing death. The amino-aciduria may have been a secondary phenomenon, just as it is the case with galactosaemia (Darling & Mortensen (5), Mortensen & Søndergaard (21).

A disease with these symptoms does not seem to have been described before; however, it cannot be excluded that Durand's (8) patient may have suffered from it. It is reminiscent of a group of metabolic disorders in which the characteristic features are that they are familial and are manifested by the absence of a single enzyme. Garrod (1908) was the first who emphasised the characteristic features of inborn errors of metabolism (alkaptonuria, albinism, pentosuria, cystinuria and porphyria). Several others have since been added to the group (17). In some of these metabolic disorders, the urine contains certain metabolites which normally occur only in very small amounts or not at all.

The suspicion that the four children suffered from an inborn error of metabolism of this type is supported by the fact that the three siblings (K.L., J. L. and E.L.) and C.L.H. were related in that they had the same great-grandparents. Further intermarriage was seen in the family of C.L.H., as consanguinity existed between his great-grandparents, who had the same grandfather.

A review of the family history did not reveal any other children who were likely to have suffered from the same disease. It is true that some deaths had occurred in other infants in the family, but the information of these was so sparse that the causes of death could not be made out.

If the disease described is hereditary, it must, in view of the fatal course, be expected that it is inherited as a recessive homozygous character, so that unaffected carriers have a defective gene. It would be conceivable that such a silent defective gene might result in biochemical manifestations without accompanying clinical symptoms. It was therefore studied if eight close relatives excreted lactose in the urine after oral administration of this substance, but paper chromatography failed to reveal lactosuria in these persons.

Nothing can be said as to the prognosis of this disease if the infants are given a milk-free diet from birth. This diet failed to save the two infants in whom it was given a trial, but the fact that proteinuria and jaundice disappeared in one of the patients when he was placed on a milk-free diet is an encouragement to make an attempt with this method as soon as the diagnosis is made, i.e. as soon as possible after birth.

If more cases of this presumably "new" disease or other disorders in which urinary sugar is a conspicuous symptom are to be diagnosed, it is of decisive importance that the urine is examined for "sugar" by a reduction method. If only a method which is specific for glucose is used (glucose-oxidase), as is done with increasing frequency, an important symptom will be overlooked.

Summary

Considerable lactosuria and amino-aciduria were revealed in two related infants. They suffered from vomiting and failed to thrive; death occurred at the age of a few weeks. Two siblings of one of the pa-

tients had exhibited the same symptoms and had died at the same age.

It is assumed that the infants suffered from a congenital, presumably hereditary, disease with diminished or abolished lactase activity—a new inborn error of metabolism.

Lactosurie et aminoacidurie chez le nourrisson. Nouvelle erreur innée de métabolisme?

Une importante lactosurie et aminoacidurie furent décelées chez deux nourrissons apparentés entre eux. Ils avaient des vomissements et ne prospéraient pas, le décès survint à l'âge de quelques semaines. Deux frères de l'un des patients avaient présenté les mêmes symptômes et étaient morts au même âge. On suppose que les enfants souffraient d'une maladie congénitale, possiblement héréditaire, qui diminuait ou supprimait l'activité lactase. Nouvelle erreur innée de métabolisme?

Laktosurie und Aminazidurie bei Kindern. Ein neuer angeborener Stoffwechselfehler?

Bei zwei Kleinkindern fand sich eine beträchtliche Laktosurie und Aminazidurie. Sie litten an Erbrechen und wuchsen nicht; der Tod trat im Alter von wenigen Wochen ein. Zwei Geschwister

eines der Patienten hatten die gleichen Symptome gezeigt und waren im selben Alter gestorben. Es wird vermutet, daß diese Kinder an einer angeborenen, vermutlich erblichen, Krankheit litten, welche die Laktaseaktivität verminderte oder aufhob — ein neuer angeborener Stoffwechselfehler?

Lactosuria y aminoaciduria en la infancia. ¿Un nuevo defecto innato del metabolismo?

En dos recién nacidos descritos se reveló una considerable lactosuria y aminoaciduria. Los niños sufrieron de vómitos y no llegaron a crecer; la muerte sobrevino a la edad de pocas semanas. Dos hermanos de uno de los pacientes habían presentado los mismos síntomas, habiendo muerto a la misma edad. Se supone que los niños padecían una enfermedad congénita, posiblemente hereditaria, que disminuía o anulaba la actividad de la lactasa — ¿un nuevo defecto innato del metabolismo?

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CASE REPORT

Congenital Thrombocytopenia Associated with Aplasia of the Radius

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Aplasia of the radius and thrombocytopenia are seen together in a rare syndrome featured by congenital hypoplastic thrombocytopoiesis and one or more congenital deformities of which the commonest is radial aplasia (9, 11, 12, 14, 17, 21, 22). Fourteen cases are described in the literature, of which 9 had bilateral radial aplasia, 4 had congenital heart disease, and 3, renal malformations. A number of patients had additional abnormalities such as cleft palate and dislocation of the hip.

Thrombocytopenia usually gives rise to symptoms already in the newborn period—often the first days of life. Megakaryocytes in the bone marrow are found to be sparse or non-existent.

The two cases described here displayed radial aplasia and thrombocytopenia, but differed from those described previously in that bone marrow megakaryocytes in both were normal or only slightly reduced.

Case 1

Boy B. L., born 13.1.54, the youngest of nine children. No family history of intermarriage, or of blood disease or congenital malformations. The patient was admitted to the Orthopaedic Clinic at the age of 2, on account of bilateral aplasia of the radius. He

had at times shown a tendency to be easily bruised. Blood count revealed thrombocytopenia and he was transferred to the Children's Hospital for investigation.

On examination:

The boy had pronounced manus vara deformity with shortening of the lower arms. Trunk and musculature appeared normal and there was no mental retardation. Nothing abnormal was found in heart or lungs. Liver, spleen, lymph glands not palpably enlarged. Skin rather pale. On the right upper arm a haematoma was noted, about 1½ cm in diameter with a few petechiae in the same vicinity.

Laboratory tests:

Hb 11.7 g % R.b.c. 4.9 millions. W.b.c. 14,000. Thrombocytes 14,000. Clot retraction was insignificantly reduced. Bleeding time 4 min. Clotting time 3½ min. The bone marrow megakaryocytes were found in reduced numbers and they were basophilic and without thrombocyte formation. Thrombocytopoiesis was regarded as hypoplastic, and surgical treatment was indefinitely postponed.

When the patient was 3 years old, the left arm was treated by 2-stage operation. There were no haemorrhagic complications. A year later, Stage 1 was carried out on the right side. Pre-operative blood count: Hb 13 g %. R.b.c. 4.2 millions. W.b.c. 6700. Thrombocytes 54,000. Bleeding time 2½ min. Clotting time 70 sec.

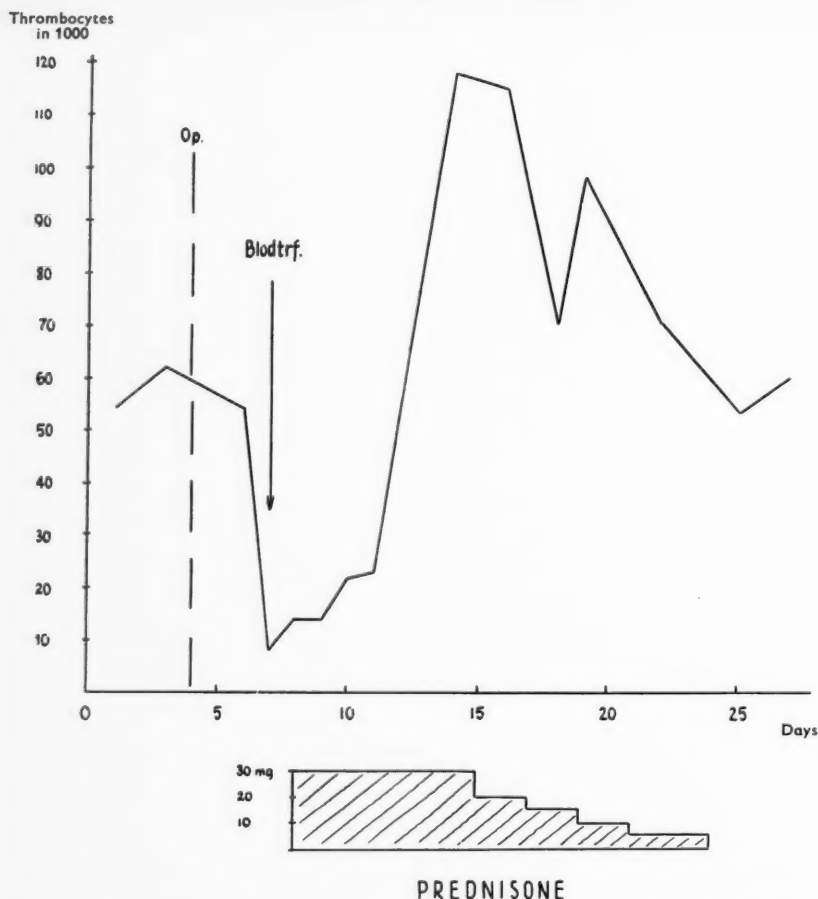


Fig. 1. Graph showing thrombocyte counts in Case 1. The platelets dropped sharply after operation, but rose steeply again with prednisone treatment.

Within a few hours of operation, he had petechiae on the trunk. Three days later he developed epistaxis, and after a sudden large haematemesis, was in a state of shock. Platelet count then was 9000, R.b.c. 2.4 millions, and Hb 9.6 g%. He was given immediate blood transfusion, and rapidly improved. He was put on to adreno-cortical steroids in large dosage. Thrombocytes rose steeply to a maximum of 119,000 but fell

again when the steroid dose was gradually reduced (Fig. 1).

Fourteen days after the cessation of steroid treatment, the bone marrow showed normal numbers of megakaryocytes, but a high proportion of small, immature, "lymphoid" forms with basophilic cytoplasm. Formation of thrombocytes was evidently scanty, but those seen were of normal appearance. No polymorphism or other de-

generative features were noted in the megakaryocytes. Erythropoiesis was somewhat low in relation to the number of immature myeloid cells, but was consistently normoblastic. Myelopoiesis was normal in amount and maturity of cells but 10 % were eosinophilic.

Four months later, the Stage 2 operation was performed. Steroid therapy was commenced the day before operation. The pre-operative platelet count was 60,000, the day after operation 11,000 and from then on showed an increase. No haemorrhagic complications occurred.

At the most recent follow-up, the boy was 5½ yrs old. He had not shown abnormal bleeding tendency. Hb was 11.3 g%. Thrombocytes 60,000. Bleeding time 5½ min, clotting time 7 min. An erythrocyte fragility test was normal. On examination of the bone marrow, the megakaryocyte shift to the left was possibly less pronounced than on the previous occasion: otherwise the picture was unaltered.

Case 2

Boy B. S., born 15.3.58. No family history of intermarriage. This patient had congenital deformity of the right hand and lower arm. X-ray showed absence of the radius and 1st metacarpal, and only a rudimentary thumb phalanx. Heart and lung examination was negative. No bruises or petechiae noted.

Blood examination revealed a marked thrombocytopenia during the first 2-3 months of life, but thereafter the platelet count was normal or only slightly lowered

(Table 1). The boy's mother had a normal platelet count. This patient has been under observation for one year. He has not shown abnormal bleeding tendency. His blood count has been otherwise normal. The first bone marrow examination was carried out at 1 year of age, and revealed a normal incidence of megakaryocytes with active thrombocyte production. Erythropoiesis was somewhat low in relation to the number of immature myeloid cells, but otherwise normal. Myelopoiesis was normal.

Discussion

Case 1 showed bilateral aplasia of the radius with chronic thrombocytopenia. Megakaryocytes in the bone marrow were mainly of immature type, and were reduced in numbers on the first examination though later occurring in normal numbers.

Case 2 had a unilateral aplasia of radius with a rudimentary thumb. Thrombocytopenia in this case was severe during the first months but later disappeared almost completely. The bone marrow was normal at one year of age. As yet the observation time is short, so the prognosis must be regarded as uncertain.

Both cases differ from those already described in that megakaryocytes were found in generous numbers in the bone marrow. The following alternatives must therefore be considered:

- i) Aplasia of radius with congenital thrombocytopenia.
- ii) Aplasia of radius with "idiopathic" thrombocytopenia.
- iii) Aplasia of radius with Fanconi's anaemia.

In *Case 1* it is not clear whether thrombocytopenia was congenital or acquired. In *Case 2* the first platelet count, at the age of 1 month, revealed thrombocyto-

TABLE 1. *Thrombocyte count during the first year of life, in Case 2.*

Age in months	Thrombocytes
1	53,000
2.5	34,000
3.5	200,000
5	150,000
8	128,000
11	221,000
12	114,000

penia, which was therefore probably congenital. The mothers of both patients had a normal thrombocyte count.

The appearance of the bone marrow was not consistent with the diagnosis "idiopathic" thrombocytopenia. In the latter condition megakaryocytes occur in normal or even increased numbers, with a predominance of mature forms and occasional giant cells (19).

Aplasia of the radius has been described in at least 7 cases of Fanconi's anaemia (6, 7, 8, 10, 13, 15, 18). But in our cases there was no hypoplasia of the bone marrow, in distinction from Fanconi's disease.

The obvious relationship between radial aplasia and congenital hypoplastic thrombocytopenia suggests that the occurrence of both radial aplasia and thrombocytopenia in our two cases is not purely coincidental. There is reason to believe that the thrombocytopenia was congenital, as in other described cases, although it was not so severe as to give rise to symptoms in the new-born period. It has been noted that in patients who survived the first year of life, a spontaneous improvement has usually occurred, and megakaryocytes have been seen in the bone marrow in increased numbers (20). It seems probable that our patients had a mild form of congenital hypoplastic thrombocytopenia, with sufficient megakaryocytes in the bone marrow already at birth, that haemorrhagic signs did not develop. The disturbance in platelet formation was not so much a shortage of megakaryocytes, as a defective maturation of these cells. In Case 1 the megakaryocytes were small and immature, answering the description given in other cases of congenital hypoplastic thrombocytopenia (11, 14). Another si-

milarity was the preponderance of eosinophils in the white cell series (11, 14).

Adreno-cortical steroid treatment in Case 1 gave good results, at least on the first occasion. This effect suggests a possible immunological aetiology for the thrombocytopenia, but it may also be compared with the unexplained improvement produced by cortisone in hypoplastic anaemia of the Blackfan-Diamond type (5).

In two reported cases the syndrome, congenital hypoplastic thrombocytopenia combined with congenital malformations, has been accompanied by sporadic congenital spherocytosis, giving rise to increased haemolysis: in Case 1 the erythrocyte fragility was tested and found to be normal.

Marked leucocytosis with significant numbers of immature cells has been observed in some cases during the first year of life (1, 9, 21). Increased erythropoiesis has also been noted, with normoblasts in the circulating blood. Extra-medullary haemopoietic foci have been discovered at autopsy, but no signs of leucaemia.

In one case with bilateral aplasia of radius, where the diagnosis hypoplastic thrombocytopenia had been made clinically, the post mortem diagnosis was congenital leucaemia (3) but was not established with certainty. The hyperactive erythro- and myelopoiesis is most probably the compensatory sequel to haemorrhage (1). In some cases it was most evident that immature cells appeared in the circulation simultaneous with, or immediately following, haemorrhage (1, 9, 21).

The clinical course of congenital hypoplastic thrombocytopenia with deformities follows no uniform pattern. Of the 14 cases reported, 6 died in the first 7 months, several as a result of cerebral haemorrhage (9). The survivors showed diminution of the bleeding tendency from

the age of 6 months to 1 year, and some showed an increased platelet count (12, 21). The oldest survivor was 19 yrs of age when last seen, and ever since infancy had been free of bleeding symptoms, despite a low thrombocyte count and the absence of megakaryocytes from her bone marrow (12). One patient had a normal platelet count 1 year after splenectomy, although the bone marrow pre-operatively showed sparse megakaryocytes, inactive in appearance (19). In two cases, on the other hand, the results of splenectomy were less encouraging (1, 9).

The reason for the simultaneous occurrence of thrombocytopenia and congenital defects has not been explained. Congenital hypoplastic thrombocytopenia can also be seen without congenital deformities, as can Fanconi's anaemia (2). It is known that the radius, and other organs which have been involved in congenital defects, develop at the same time as the megakaryocytes, so it has been suggested that an early injury to the foetus can be the common cause (1, 21). A genetic defect is another possibility: Gross *et al.* have described the condition in two siblings. In other cases it has been impossible to discover congenital defects or blood disease among relatives, in distinction from Fanconi's anaemia.

It has been suggested that congenital hypoplastic thrombocytopenia might be a particular variety of Fanconi's anaemia (9, 12). There are, however, obvious distinctions. The different family history has already been pointed out. Congenital hypoplastic thrombocytopenia usually gives rise to symptoms in early infancy, whereas Fanconi's anaemia first appears at the age of several years. A marked leucocytosis during the early months is also typical of congenital

hypoplastic thrombocytopenia. Fanconi's anaemia is a slowly progressive disease, whereas those cases of congenital hypoplastic thrombocytopenia who survive the first, critical period usually improve spontaneously.

In orthopaedic literature concerning malformations of the radius, the occurrence of pancytopenia—i.e. Fanconi's anaemia—has been noted: but not congenital hypoplastic thrombocytopenia (4, 16). Many cases of radial aplasia appear however to have died in early infancy, and might possibly have had hypoplastic thrombocytopenia as cause of death. It is possible that routine blood examination, including platelet count, in all children with malformations of the upper extremities might reveal a higher incidence of blood dyscrasias than has been realised to date.

Acknowledgements

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Summary

Two cases are described of aplasia of the radius accompanied by thrombocytopenia. They differ from earlier reported cases of this syndrome in that their bone marrow megakaryocytes were found in normal or slightly reduced numbers. There were no signs of bleeding in early infancy. One child developed severe haemorrhage following operation. Cortisone produced definite improvement in the platelet count, which might be compared with its effect in hypoplastic anaemia. The second child only displayed thrombocytopenia during early infancy, and at no time had haemorrhagic symptoms.

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Hypophosphatasia

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Introduction

Hypophosphatasia is the term applied to a chronic skeletal disease that affects principally children. It is characterized by defective rebuilding and mineralization of bone and combined with a marked reduction in the serum alkaline phosphatase activity. It is a rare disease. Rathbun (9) ten years ago was the first to describe it under the above heading. Since then 35 cases in all have been published (Fraser) (5) one of which in Sweden (Engfeldt & Zetterström) (4). There is, however, no doubt that the disease has been mentioned also in the earlier literature, though by less adequate terms. Thus, Chown (2) 1935 described, for instance, under the heading renal rickets 2 cases in sisters (whose parents were cousins) who died at the age of 3 and 6 months, respectively. The case reports, as well as the objective findings, are so typical as to justify the diagnosis of hypophosphatasia, although no phosphatase activity was examined. As a rule the disease is not manifested until some time after birth in spite of its being congenital. In one of the cases of McCance, Fawcett, Barret & Morrison (7) (Case 2) skeletal changes were observed already

in utero, as also in one of Currarino, Neuhauser, Reyersbach & Sobel (3) cases (Case 2). In exceptional instances the disease does not appear until later in childhood. In general, it has been found that the earlier the onset of the disease, the more severe the symptoms and the less favourable the prognosis. In 5 of the cases in which the disease had an intrauterine onset the patients died soon after birth of respiratory insufficiency (Currarino *et al.*). When the disease sets in somewhat later in infancy to begin with certain general symptoms are manifested, such as anorexia, tendency to vomiting, obstipation, poor weight gain and slow growth in length. A rise of temperature, not infrequently periodic, without any signs of infection may be noted, sometimes attacks of cyanosis, in serious cases also convulsions. The eruption of the teeth usually takes place in normal time, but the teeth often loosen prematurely and fall out.

Symptoms and Signs

The state of nutrition in hypophosphatasia is more or less unsatisfactory, the musculature is sometimes hypotonic, the complexion pale. Blue scleras have occa-

sionally been observed (Fraser, Schlesinger *et al.* (10)). The objective findings refer above all to the skeleton. The head is generally globular, soft with (apparently) very wide sutures, sometimes almost boneless, and the large fontanelle bulges conspicuously. Marked costochondral beading and epiphyseal enlargements, resembling those of rickets, are seen, and in some cases, in slightly older children, kyphosis. To this may be added curvatures and deformities as the result of healed spontaneous fractures. The roentgenologic findings are characteristic, being due to defective calcification of the pre-osseous cartilage and of the rebuilt bone substance, irrespective of enchondral or secondary formation of bone (McCance *et al.*). In the cases in which the disease was manifest already in the newborn period, large parts of the skeleton are found to be entirely uncalcified, particularly in the skull, where the parietal and temporal bones might be reduced to small plaques of bone. Gradually a rounded osseous prominence appears at the site of the bulging fontanelle, and, in the 2nd year of life, signs of premature craniosynostosis. In the long bones the provisional calcification zone is only vaguely discernible, the epiphyseal lines are wide and irregular and the metaphyses markedly poor in calcium, spotty and streaky. From the almost demineralized metaphyses a gradual transition to relatively normally mineralized diaphyses is observed. The contours of the latter are, however, often irregular and fuzzy owing to subperiosteal ossification.

Involvement of the kidneys is usual, in advanced cases, with hypertension, as in Engfeldt & Zetterström's case (a girl of 6

months with 220 mm Hg), slight proteinuria and signs of reduced function with lower concentration capacity and azotemia. A moderate anemia of normochromic type is not infrequent. Moderate hypercalcemia of 12–14 mg % forms part of the picture (maximum value 18.5 mg % reported in MacDonald & Shanks' (8) Case 1), while the serum inorganic phosphorus is normal.

However, the principal finding is a considerably reduced serum alkaline phosphatase activity. This is normally 10–20 Bodansky units (4–8 mM) in infants, in older children 5–10, whereas in these cases the values are so low as 2–3 units and under, in Rathbun's case even at times not at all ascertainable. There is no actual relation between the degree of severity of the disease and that of reduced phosphatase activity. Rathbun found that the phosphatase activity was reduced simultaneously also in other tissues such as the skeleton, kidneys, and mucous membrane of the intestine. A generalized hypophosphatasia, accordingly, seemed to be present, as was, moreover, confirmed later by several investigators, among whom Engfeldt & Zetterström may be mentioned. McCane *et al.* ascertained such a low activity in the skull as approximately 1 % of the normal, and demonstrated a reduced phosphatase activity also in the liver. From later histo-chemical observations it emerges that, as regards the kidneys, the enzyme in them is localized to the proximal section of the tubules (in which resorption of glucose takes place), while the distal sections do not show any phosphatase activity, which applies also to the glomerules (quot. Lanman (6)).

In 1954, Fraser *et al.* and McCance *et al.*,

irrespective of each other, discovered in cases of hypophosphatasia a substance in the urine which had not been observed earlier, viz. *phosphorylethanolamine*, a finding that was later confirmed by others (Dent & Cuworth in 6 cases, Harris & Robson in 14 (Fraser)). The occurrence of that substance in the urine is not, however, pathognomonic, having lately been observed occasionally also in celiac disease, scurvy and hypothyroidism, all morbid conditions involving a tendency towards low serum alkaline phosphatase activity. The reason why phosphoethanolamine appears in the urine of these patients is, according to Fraser, that there is insufficient phosphatase to hydrolyse the ester phosphate linkage, thus resulting in its accumulation in the blood. According to this theory, phosphoethanolamine should be one of the naturally-occurring substrates of alkaline phosphatase. In agreement with this, McCance recently showed that alkaline phosphatases deriving from different normal tissues are capable *in vitro* of hydrolyzing synthetic phosphoethanolamine (Fraser).

From a patho-anatomic point of view, all growing cartilage, e.g., epiphyseal cartilage, costochondral junctions, etc., disclose conspicuous changes in the form of increased width of the proliferating cartilage, irregularity of the cell column formation and of the penetration of hypertrophic cells by the marrow. Long tongues of cartilage persist in it. In the metaphyses the normal architecture is more or less replaced by osteoid, which often surrounds islands of uncalcified cartilage. Osteoblasts and osteoclasts seem normal as regards the morphology and quantity. In a microradiographic examination of a

girl of 10 months, Engfeldt & Zetterström found the development of the osseous tissue extremely retarded. The diaphyses resembled on the whole those of the newborn both as regards structure and mineralization. The Haversian systems in compact bone had a varying density of calcium salts. The lowest mineralization was noted in the young, newly formed systems, the highest in old bone tissue surrounding the Haversian systems. The new-formed bone tissue lacked cementing lines and showed sparse resorption cavities.

In the kidneys changes are regularly seen that indicate a low-grade nephritis and scarring (Currarino *et al.*). Deposits of calcium salts are observed in the tubular epithelium and in the surrounding interstitial tissue, sometimes also calcium casts. In no single case was this nephrocalcinosis sufficiently marked to be observable by the ordinary radiography. However, by means of microradiography Engfeldt & Zetterström managed to demonstrate this clearly in their case, revealing that the precipitation of calcium salts was most pronounced in the inner third of the cortex. The distribution of the calcium salt deposits resembled that noticed in vitamin D intoxication in rabbit.

Etiology

It was early suspected that a genetic factor was of etiologic significance in hypophosphatasia, this being confirmed by later observations ("Inborn error of metabolism"). Carriers among parents and relatives have been identified by the low values of the phosphatase activity, and recently the ascertainment of the phosphorylethanolamine in the urine has been used for the same purpose. Fraser found,

in 12 families in which this disease had appeared in 16 persons of 21, a reduced alkaline phosphatase activity; these sixteen therefore were regarded as heterozygotes. In spite of incomplete data concerning the sibs, it emerged that 9 out of 34 sibs of the probands were affected by the disease, i.e. 26.4%, a figure that approximates $\frac{1}{4}$, and out of 13 healthy sibs examined 9 were heterozygotes and 4 normal, which corresponds approximately the 2:1 ratio expected. (The preponderance of the female sex in this compiled material (21 against 14) was too small for the deviation from 1:1 sex ratio to be statistically significant.) The disease may, accordingly, be said to be genetically determined, being inherited by the action of an autosomal recessive gene.

Course

When the onset of the disease occurs in the first three months of life, the patients do not as a rule survive. Thus, according to a compilation by Fraser, 10 of the 16 children belonging to that group died. After that age the course of the disease becomes gradually milder and, when the children have reached the age of 6 months at the onset all survived according to the same record. In these cases the skeleton gradually acquires an increased calcium content, in spite of the persisting low alkaline phosphatase activity. The primarily bulging fontanelle, which must be regarded as the result of a disparity between the rate of growth of the brain and that of the cranium, forms a rounded osseous prominence. A premature craniosynostosis is often seen in the second year of life, occasionally causing a compression of the optic nerve with subsequent blind-

ness. (Craniotomy owing to papilledema was performed in Case 1 of Schlesinger *et al.*) Occasional convulsions may conceivably have the same cause (Fraser) as also a retarded motorial development. Although other skeletal changes, i.e. even in untreated cases, may heal fairly quickly, as happened in a case reported by Currarino *et al.* in which the healing process started at the age of 8 months and resulted in a normal appearance of the long bones at 20, these changes do generally remain for much longer, up to the age of 3-4 years. According to Fraser, 4 cases of hypophosphatasia have been described in adults, being manifested by an increased brittleness of the bones. In at least 2 of these cases the disease was said to have started in childhood. As this has so recently been detected, reliable data are not yet available concerning the long term prognosis.

Therapy

Several cases of hypophosphatasia have been treated with vitamin D in large doses owing to a superficial likeness to vitamin D-resistant rickets, professedly with some improvement (Schlesinger *et al.*). In the light of recent observations of the course in untreated cases, the effect of such a therapy seems, to say the least of it, doubtful. The fact that it may, on the contrary, be injurious is evident from the quick development, in several instances, of a severe hypercalcemia. In a case reported by Sobel *et al.* (quot. Currarino *et al.*), concerning a girl of 4 months, in the course of this treatment extensive calcifications of the soft tissues were not infrequently observed. The patient died at the age of 2 years and 5 months and autopsy disclosed calcifications also in the heart and kidneys.



Fig. 1. Patient E. S. at 7 months of age. Note: bulging fontanelle.

Cortisone treatment seems more justified, to judge from a case described by Fraser which had a perinatal onset. The dose was 37.5 mg daily, and as soon as 3 weeks after the treatment had been started mineralization was observed at the zones of provisional calcification. After another 2 months the mineralization of the metaphyses, as well as subperiosteally, was so considerable that the bones had an almost normal appearance. This was no transient effect, as is evident from the simultaneous doubling of the alkaline phosphatase activity and the decrease in the blood calcium. At the time of publishing the case, treatment had continued for 1½ year, and the patient seemed healthy but grew slowly. Blood calcium was normal, but the alkaline phosphatase activity was only slightly higher than prior to treatment. Swoboda (11), on the basis of a hypothesis propounded earlier accord-

ing to which the alkaline phosphatase activity is increased by magnesium, administered a magnesium salt (1-2 gram daily) in his case of hypophosphatasia. Though a continuous improvement in the skeletal changes was seen, there was no effect on the low phosphatase value nor on the content of magnesium in the serum (which was at the lower limit of the normal). Accordingly, a causal connection seems very doubtful.

As a contribution to the so far scant knowledge of this condition a typical case of hypophosphatasia, recently treated at the Children's Hospital in Gävle, is reported.

Elisabeth S., born 24/4 1957, was treated at the Westergren Children's Hospital in Gävle during the period of 4/9-23/12 in 1957 under the diagnosis of *hypophosphatasia + anemia* (J 464/57). She is the only child of healthy parents. No known consanguinity.

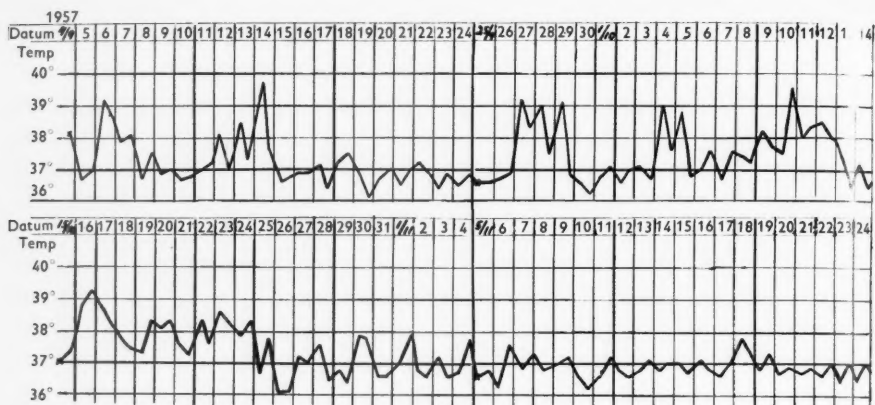


Fig. 2. The temperature curve.



Fig. 3. Radiograph of head. Age 3 months. Coronal suture appears greatly widened (a good 2 cm) because the adjacent parts of the frontal and parietal bones are entirely uncalcified. Note: prominent soft tissue parts at site of large fontanelle.

Parturition normal. Birth weight 4110 g. Breast-fed for 2 months, then mixed diet to the age of 3½ when she was given Fin-dus gruel 160 g × 5. In the month prior to admission, vomiting on and off, particularly in the mornings. Normal evacuation. During the first month of life poor weight gain (she weighed 4020 g on June 5) but after that satisfactory. In the week prior to admission,

she had some coughing and a cold, seemed irritated. On examination at a Children's Welfare Centre on September 4, she was found to have a temperature of 38.5°C and the fontanelle was tense (Fig. 1). She was therefore hospitalized.

The patient seemed irritable, especially when handled. Weight 5480 g, height 65 cm. Temp. 38.1°C. No dyspnoea. Pale complexion. Skin tonicity and musculature fairly normal. Internal organs without remark. Head circumference 40 cm. The large fontanelle, which measured 4 × 4 cm, was tense and markedly bulging, sutures very wide (Fig. 3). Moderate craniotabes, strong costochondral beading and slight widening of the epiphyses which by degrees became more marked. The fundus of the eyes without remark, the reflexes likewise. Urine was free from albumin, but contained on some occasions traces of sugar (max. 0.34%), sediment 5-6 white blood corpuscles per field of vision and isolated hyaline casts. Urine calcium 8.8 mg %, urine phosphorus 15.6 mg %. Blood: Hb 67 % = 10.2 g %, red blood corpuscles 3.80 mill., white blood corpuscles 13,300, 7300 of which were polynuclear and 6000 mononuclear. Micro ESR 35. Blood calcium 12.8 mg %, blood phosphorus 5.1 mg %, alkaline phosphatase activity 3 Units = 1.2 mM. Non-protein nitrogen 50 mg %. Blood sugar 14

mg %. Ventricular puncture gave slightly sanguinolent fluid under low pressure. Cerebrospinal fluid was clear and colourless after centrifugation. Pandy och Nonne positive. Albumin content 98 mg %. White blood corpuscles 176, erythrocytes 20,000 per mm³. Lumbar puncture 3 weeks later gave clear, colourless fluid under initial pressure 200 mm. Pandy and Nonne negative. Albumin content 36 mg %. White blood corpuscles 4, red 400 per mm³. WR and Meinicke negative in the blood as well as in the CSF. Dye test according to Sabin & Feldman, was negative as was also the complement fixation test with toxoplasma antigen.

Roentgenologic examination of the skeleton showed marked changes with strongly reduced calcium content, particularly in the metaphyses. Considerable diastasis occurred between the parietal and frontal bones. The collum femoris had an irregular structure with fairly coarse trabeculae in an area about 5 mm broad next to the epiphyseal line. The distal ends of the femora showed similar changes with a frayed zone 5 mm broad with irregular calcium-dense trabeculae (Fig. 4). Proximally to the latter, a relatively calcium-deficient zone, a good cm broad, followed by a denser part which is separated from the rather calcium-dense diaphyses by another thin area. Also the pea-sized epiphyseal nuclei were deficient in calcium. Thin periosteal deposits along the diaphysis. The tibia and fibula showed similar changes with two band-shaped, calcium-poor parts in the metaphyses, separated from each other by one more dense in calcium. Here too periosteal deposits were found. In the talus and calcaneus more calcium-dense layers were noted close to the articular surfaces, particularly at the distal articular surface of the talus which was cut off from the rest of the talus by a thinner zone. The nucleare had a fragmented nucleus. The epistula of the metatarsal bones disclosed similar changes, in miniature, to those in other epiphyses, with a thin calcium-dense zone distally, and proximally two band-shaped rarefactions, 1 mm broad. In the humerus, largely the same changes as in the



Fig. 4. Radiograph of lower extremity. Age 5 months. In the distal femoral metaphysis a frayed zone $\frac{1}{2}$ cm broad with irregular calcium-dense trabeculae. Proximally to that a calcium-deficient part, a good cm broad, followed by another calcium-dense part. Epiphyseal nucleus poor in calcium. Tibial and fibular metaphyses show changes similar to those in femur. Periosteal deposits.

femur. In the radius and ulna the same changes as in the tibia and fibula. The periosteal deposits were insignificant, however, in the bones of the upper extremity. The sternal ends of the ribs were widened and otherwise had the same appearance as the epiphyses of the long tubular bones. Serum albumin 6.5 %. Electrophoresis: albumin 52, globulin α_1 5, α_2 15, β 14, γ 14 rel. %



Fig. 5. Radiograph of head. Age 1 year 4 months. Craniosynostosis. Bulging osseous prominence at site of large fontanelle. Highly increased convolucional markings.

In the urine phosphoethanolamine was demonstrated by means of paper chromatography (at investigations at the medico-chemical institutions of Karolinska Institutet, Stockholm, and the University of Gothenburg).

The patient belonged to the blood group combination A_1 Rh(+) type Rh₂, the mother A_1 Rh(-), but no irregular antibodies occurred. Blood sample from mother contained 9.3 mg% calcium, 4.1 mg% phosphorus, alkaline phosphatase activity 4 Units. Blood sample from the father 10.4 mg% calcium, 2.9 mg% phosphorus, alkaline phosphatase activity 2 Units.

Course. The patient had, during the first 1½ month, a recurring temperature of 39.1°–39.7° not less than 7 times, each time lasting for 2–3 days, without any simultaneous signs of infection (Fig. 2). She was irritable, particularly when handled. Her appetite was not very good, she vomited often and the weight kept stationary at 5500 g for 2 months. At first she was given Findus gruel but, as she was constipated, obtained milkotal which

she did not like very much. Therefore, changed to Baby O K, and her food was successively supplemented with crusts, mash and fruit-juice soup, so that she finally obtained a mixed small child's diet. Further, the nutrient vitamin compound Glaxo was administered. She was otherwise treated with AD-vimin 15 drops \times 1 and when temperature set in with magneeyl. After 2 months her condition began to improve, and her temperature became normal. The tenderness of the body disappeared and the patient became bright and cheerful. The appetite improved, the vomiting ceased, the stools were normalized, and her weight began to increase. At the same time, the cranial sutures successively diminished, being closed at the discharge from Hospital. The large fontanelle measured then $1\frac{1}{2} \times 1\frac{1}{2}$ cm, the nearest surrounding part of bone forming a rather conspicuous prominence corresponding to the original soft tissue bulging. Marked costochondral beading and epiphyseal enlargements remained. Blood calcium fell in barely 2 months to the normal value 9.4 mg%, while the alkaline phosphatase activity simultaneously increased by 8 Units. The non-protein nitrogen value remained elevated for 3 months but then decreased to normal (26 mg%). Blood values increased to Hb 82% = 12.5 g%, red blood corpuscles 4.40 million. Micro-ESR which was at a maximum of 46 mm, fell to 13 mm/h. The patient was discharged in comparatively good condition after having increased 680 g in weight, i.e. to 6160 g.

After that the patient felt fairly well and developed satisfactorily, though the motorial development was retarded. She was able to sit at the age of 9 months, to rise to sitting position at the age of 11 months, but was still unable to walk at the age of 1 year and 10 months. The first teeth appeared at 1 year of age. Mental development, as well as that of speech, quite undisturbed, so that at the age of just 2 she pronounced 3-word sentences. Since radiography of the skull at the age of 16 months showed premature synostosis of all the sutures (Fig. 5), and very pronounced convolucional impressions,

craniotomy was advised and the patient was referred to the neuro-surgical department of the Serafimer Hospital. She was treated there from January 13 to February 20, 1959. Encephalography revealed forward-downward inclination of the lateral ventricles, as in oxycephalia. Craniotomy was performed in two stages, one parasagittally on either side of the median line, the other frontally in the frontal region. Postoperative course without remark. The patient was admitted for postoperative treatment at the Children's Hospital in Gävle where she stayed from February 20 to March 10, 1959. The general condition was good. Weight 9020 g. Height 76 cm. Head circumference 45 cm. At the site of the fontanelle a large, flat prominence was noticed, of $4 \times 5 \times 2$ cm. Surgically applied sutures, 1 cm wide, were palpated parasagittally and frontally. Marked costochondral beading was still evident as well as epiphyseal enlargements. Non-protein nitrogen 28 mg%. Blood calcium 10 mg%. Blood phosphorus 6.2 mg%. Alkaline phosphatase activity 2 Units (0.8 mM). Radiography disclosed a considerable increase in the volume of the calotte after craniotomy. The epiphyseal changes showed rather pronounced regression with increased sclerosis (Fig. 6). The patient was allowed to exercise in a go-cart during her hospital stay, and was able to kick her way about in it at discharge.



Fig. 6. Radiograph of lower extremity. Age 1 year 10 months. The epiphyseal changes show rather pronounced regression with increased sclerosis.

This was, accordingly, a typical case of hypophosphatasia. The skeletal changes, particularly as seen in the radiogram, the bulging fontanelle in the absence of elevated intracranial pressure, with simultaneous hypercalcemia are characteristic of this affection. The diagnosis was confirmed by the strongly reduced alkaline phosphatase activity and by the ascertainment in the urine of phosphoethanolamine. The disease is not heard of in the family, though the parents must, according to the above observations, be assumed to be

carriers (heterozygotes). The father also had a low phosphatase activity that was at the lower limit of the normal value. In the urine from the parents no phosphoethanolamine could be detected.

Pyrexia, not uncommon in the initial phase of hypophosphatasia, was a promi-

nent symptom in this case. It lasted for one month and a half, being of a rather undulating type (Fig. 2). As pointed out by Ask-Upmark (1), in particular, such a pyrexia of the Pel-Ebstein type is not infrequently to be found in conditions in which the bone marrow *viz.* the reticuloendothelial system are involved in the pathophysiologic mechanism. Hyperparathyroidism is quoted as an example, causing as it does extensive rarefactions in the skeleton. From this point of view, it appears significant that in hypophosphatasia, which is characterized also by the fact that large parts of the skeleton are uncalcified, the same kind of pyrexia is observed. Although it is impossible to ascertain the exact mechanism of the pyrexia, it may be stated that this fever remained as long as the hypercalcemia, i.e. it disappeared only when the skeleton began to recover its capacity of calcium absorption from the blood.

As usual in hypophosphatasia, signs of renal involvement (azotemia) were noted also in the present case. The cause of this complication is no doubt to be traced to the hypercalcemia, i.e. the mechanism is analogous to that of renal injury owing to hyperparathyroidism and hypervitaminosis D. As the calcium balance is positive, the bone resorption abnormally reduced (Engfeldt & Zetterström), and every sign of a parathyroid involvement is lacking, there is no proof that the increased quantity of circulating calcium in the blood should have a skeletal origin. The hypercalcemia in hypophosphatasia is probably due to an incapacity to deposit the mineral salts in the skeletal system at simultaneous normal calcium resorption in the intestine (Fraser). It is quite likely

that the glycosuria ascertained in the initial stage in the present case was a manifestation of a defective local *viz.* renal phosphatase activity (through reduced glucose-resorption in the tubules), though sufficient to prevent a permanent renal glycosuria (cp. Lanman).

In spite of the fact that the disease had such an early onset as in the 3rd month of life, the course was favorable with only symptomatic treatment including the administration of vitamin D, which was strictly limited to the general prophylactic dose. When the blood calcium had decreased to the normal level, also the renal function was restored, and from the 7th month of life a continuous reparation of the skeletal changes took place. Owing to premature synostosis of all the sutures in the skull, craniotomy was performed with good results. In spite of the considerable skeletal changes remaining at the age of 2 years, the prognosis may, no doubt, be regarded as favorable, particularly in view of the altogether undisturbed mental development.

Summary

A typical case of hypophosphatasia is described in a girl of 4 months of age. Pronounced skeletal changes, hypercalcemia and signs of impaired renal function were noted. The alkaline phosphatase activity was as low as 3 Units (= 1.2 nM) and phosphoethanolamine was ascertained in the urine. The disease took a favourable course with merely symptomatic treatment, special attention being paid to avoiding vitamin D in therapeutic doses. From the 7th month of life, the symptoms showed a tendency to subside, the blood calcium fell to normal, the renal function

was restored, and a gradual reparation of the skeletal changes could be observed from then on. However, at the same time a premature synostosis of the sutures of the calotte occurred. Craniotomy was therefore performed with good results at

the age of 1 year and 9 months. It is of practical importance to distinguish this condition from that of the ordinary rickets and the so-called vitamin D-resistant rickets, as high doses of vitamin D has a purely deleterious effect.

Hypophosphatasie

Un cas typique d'hypophosphatasie chez une petite fille de quatre mois est présenté. On note des changements squelettiques prononcés, une hypercalcémie et les signes d'une fonction rénale défectueuse. L'activité phosphatase alcaline était descendue jusqu'à trois unités et on décelle la présence de phosphoéthanolamine dans l'urine. L'affection prit un cours favorable grâce à une médication symptomatique. On prit particulièrement soin d'éviter la vitamine D en dose thérapeutique. A partir du septième mois, les symptômes tendent à disparaître, la quantité de calcium dans le sang redevint normale la fonction rénale fut rétablie et à partir de ce moment on put observer une restauration graduelle des changements squelettiques. Cependant, au même moment se produisit une synostose prématurée des sutures du crâne. Une craniotomie fut faite avec de bons résultats à l'âge d'un an et neuf mois. Il est extrêmement important au point de vue pratique de distinguer cet état d'avec le rachitisme ordinaire et d'avec le rachitisme résistant à la vitamine D, puisque de fortes doses de vitamine D ont un effet purement nuisible.

Hypophosphatasie

Es wird ein typischer Fall von Hypophosphatasie bei einem Mädchen von 4 Monaten beschrieben. Es wurden starke Skelettveränderungen, Hyperkalzämie und Anzeichen von Nierendysfunktion beobachtet. Die Alkaliphosphatase betrug nur 3 Einheiten und im Urin wurde Phosphoethanolamin sicher nachgewiesen. Die Krankheit nahm mit rein symptomatischer Behandlung einen günstigen Verlauf, wobei besonders darauf geachtet wurde, das Vitamin D in therapeutischen Dosen ganz zu vermeiden. Vom 7. Lebensmonat an zeigten die Symptome eine Tendenz zum Nachlassen, das Blut-

kalzium ging auf seinen normalen Spiegel zurück, die Nierenfunktion wurde wiederhergestellt; von diesem Zeitpunkt an konnte auch eine allmähliche Wiederherstellung der Skelettveränderungen beobachtet werden. Gleichzeitig stellte sich jedoch eine vorzeitige Synostose der Kalottennähte ein. Im Alter von 1 Jahr und 9 Monaten wurde daher mit gutem Erfolg eine Craniotomie durchgeführt. Es ist praktisch wichtig, diesen Zustand von der gewöhnlichen Rachitis und der sogenannten Vitamin-D-resistenten Rachitis zu unterscheiden, da hohe Dosen von Vitamin D nur eine schädliche Wirkung haben.

Hipofosfatasia

Se describe un caso típico de hipofosfatasia en una niña de 4 meses. Se observaron pronunciadas modificaciones en el esqueleto, hipercalcemia y signos de función renal deficiente. La actividad de la fosfatasa alcalina no alcanzaba más que 3 unidades y se descubrió, con seguridad, fosfoetanolamina en la orina. La enfermedad tomó un transcurso favorable con sólo el tratamiento sintomático, prestándose especial atención a evitar la vitamina D en las dosis terapéuticas. Desde el 7º mes de vida, los síntomas mostraron una tendencia a relajarse; la calcemia bajó al nivel normal; se restableció la función renal y desde entonces pudo observarse una reparación gradual de las modificaciones esqueléticas. Sin embargo, al mismo tiempo sobrevino una sinostosis prematura de las suturas de la calota. Por lo tanto, se procedió a craneotomía, con buen resultado, a la edad de 1 año y 9 meses. Es de importancia práctica distinguir esta enfermedad, tanto del raquitismo ordinario, como del llamado raquitismo resistente a la vitamina D, ya que las elevadas dosis de vitamina D no tienen sino un efecto puramente deletéreo.

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SUMMARIES OF SUPPLEMENTS

Observations on ABO Incompatibility Between Mother and Infant

by GEOFFREY C. ROBINSON, HENRY G. DUNN and LEI CHING WONG

(Supplement 120)

Part I. Patterns of Maternal ABO Antibodies in Unselected Pregnancies

After preliminary serological investigation of 109 male and 63 female random Group O blood donors a systematic prospective study of serological findings in 154 Group O women attending a Prenatal Clinic was established. They were subsequently found to be divisible into 100 homospecific and 54 heterospecific pregnancies. The levels and changes of different forms of anti-A in 49 and of anti-B in 20 homospecific pregnancies were compared to those of the incompatible maternal antibodies in the heterospecific pregnancies.

The titres of anti-A and anti-B agglutinins in saline at room temperature were found to cover a wide range and to be approximately equal initially in homospecific and heterospecific pregnancies and in primigravidae and multigravidae.

In homospecific pregnancy the titres in saline showed a slight rise, presumably of an anamnestic nature, after delivery in a small proportion of mothers (10 out of 49, or 20.0% in the case of anti-A). In heterospecific pregnancies this postpartum rise of titre was considerably more marked and frequent, occurring to a significant degree in 14 out of 34 of O-A cases;

(41.1%) in some of these a slight rise was beginning to occur during pregnancy.

Titres of anti-A and anti-B agglutinins in albumin at 37°C followed a somewhat similar pattern. Prenatally for anti-A, this titre exceeded that of saline agglutination by two or more dilutions in 6 of 36 homospecific and 5 of 37 heterospecific O-A pregnancies, thus suggesting the presence of an incomplete agglutinin. Postnatally for anti-A, such a difference in titres was found in 5 of 39 homospecific and in 8 of 36 heterospecific O-A pregnancies.

Anti-A hemolysins were found in about three-quarters of homospecific and O-A heterospecific pregnancies. After delivery their incidence rose to 37 out of 43 (81%) homospecific and to all of 23 (100%) heterospecific pregnancies; the changes in anti-B hemolysins were less marked. When tests for maternal hemolysins were performed against fetal instead of adult A₁ cells as recommended by Crawford and colleagues (41), hemolysis was usually less marked and high titres (8 or more) were more significant in terms of possible risk to the infant.

Residual agglutination in albumin and a positive indirect antiglobulin test against A cells were demonstrated in the maternal sera in about one-third of homospecific pregnancies and in a slightly, but not

significantly, larger proportion of heterospecific cases. These antibodies were also found singly in another one-fifth of the mothers, so that less than one-half of the women had neither form of immune anti-A. In 3 of 54 heterospecific pregnancies such immune anti-A arose *de novo* after delivery. The titres and incidence of these immune antibodies did not change markedly postpartum but there was a trend for increased amounts of group specific substance to be required for neutralization, particularly in heterospecific pregnancy.

During pregnancy about one-fifth of the women in the homospecific and one-third in the heterospecific group had all three forms of immune anti-A (hemolysin, positive indirect antiglobulin test after neutralization and residual agglutination in albumin) and only about one-sixth of each group were negative for all these tests while the rest appeared "partially immune", commonly owing to the presence of hemolysins. After delivery there was a slight change towards a higher incidence of immune antibodies in homospecific pregnancy and a more definite one in heterospecific cases where 9 of 23 mothers eventually had all three forms of immune anti-A and all had the anti-A hemolysin.

The findings are discussed in relation to those of other workers.

Part II. The Transfer of Maternal Anti-A and Anti-B Antibodies to the Infant

In homospecific O-O pregnancy anti-A and anti-B agglutinins were found to reach the cord blood in the great majority of cases, both as demonstrated in saline at room temperature and in albumin at 37°. The level of saline-agglutinin at room

temperature in the cord blood was, however, considerably more depressed in comparison to the maternal titre than that of the agglutinin demonstrated in albumin at 37°. In more than half the cases the titre of agglutinin in albumin in the cord blood exceeded that of the saline-agglutinin. The direct antiglobulin test was uniformly negative in the cord blood of homospecific infants.

In heterospecific pregnancy incompatible saline-agglutinin was only found in the cord blood of 3 out of 55 infants, and at very low titre. One of the 3 babies concerned had a positive direct antiglobulin test. Agglutinin in albumin was demonstrated in 28 of 46 cord bloods tested, but was present in much lower titre than in homospecific pregnancy. Five of the 8 heterospecific infants who had agglutinins in albumin to a titre of 8 or more also had a positive direct antiglobulin test. The indirect antiglobulin test was positive in about half the infants in whom it could be performed. Virtually all the infants who had a positive direct antiglobulin test were included among those with a positive indirect test, and they represented about 60 % of that group.

The direct antiglobulin test was positive in 15 cases among the 55 heterospecific infants. This represents a larger proportion than that encountered by other workers and is explained by the fact that cord blood was tested routinely and that serial dilutions of native antiglobulin serum were used in addition to commercially available serum. Optimal results were obtained when the native serum was diluted 1:100.

When the positive direct antiglobulin test in the infant is related to the maternal serological status, it is found to occur most

frequently when the mother has all the various forms of immune ABO antibodies (hemolysin, residual incomplete agglutinin and positive indirect antiglobulin test after neutralization). In regard to individual maternal antibodies the closest connection appears to be with a positive maternal indirect antiglobulin test after neutralization, for in the presence of this phenomenon the infant had a positive direct antiglobulin test in about half the cases.

Part III. Clinical and Laboratory Findings in Heterospecific Pregnancy with a Note on the Incidence of ABO Hemolytic Disease

With the use of a titration method applied to native antiglobulin serum, 15 out of 55 infants born of heterospecific pregnancy were found to have cord blood giving a positive direct antiglobulin test. Neither the whole group of heterospecific infants nor the sub-group with a positive direct antiglobulin test differed significantly from homospecific infants in regard to the mean hemoglobin concentration, serum bilirubin level or mean reticulocyte count. However, by laying down certain serological, clinical, biochemical and hematological criteria of hemolytic disease, it was possible to separate a group of 8 infants with disease in the heterospecific group who differed significantly from homospecific infants and even from the other heterospecific infants with a positive direct antiglobulin test in regard to their mean cord serum bilirubin level. Details of the clinical status, hemoglobin concentration and serum bilirubin levels and other hema-

tological data in regard to these affected infants are given. The serological pattern in their mothers is also tabulated.

The occurrence of 8 cases of hemolytic disease in the offspring of 154 random Group O mothers mated with fathers of unknown ABO Group represents a disease incidence of 5.1%. On the basis of this incidence in heterospecific pregnancy it is calculated that the disease probably occurs in about 2.2% of all pregnancies and in 11.1% of "dangerous matings" when the mother belongs to Group O and the father has an A₁ or B agglutinin or both.

It is agreed that the disease is usually mild; among 55 heterospecific infants only one required a replacement transfusion, and one had to have two simple transfusions for late anemia.

Part IV. Hemolytic Disease of the New-born

A detailed analysis of 37 cases of hemolytic disease due to ABO incompatibility is presented, with particular reference to the serological findings. These 37 infants were the offspring of 36 Group O mothers, and all satisfied the criteria for ABO hemolytic disease as laid down in a previous section of this paper. Thirty of them belonged to Group A and 7 to Group B. Nine were first-born children. The clinical manifestations corresponded closely to those described in other series. The main presenting symptom was early jaundice, and its severity largely determined the prognosis and treatment. Significant anemia was also present in 10 of the infants, but was usually mild. The hematological findings are discussed; the

almost universal presence of spherocytosis, the occurrence of reticulocytosis in over half of the cases tested and the somewhat less frequent finding of a raised nucleated red cell count are described. The changes in serum bilirubin levels are also outlined.

Twelve of the 37 infants received replacement transfusions (repeated in three instances), and one further child received two simple transfusions. No fatalities and no cases of kernicterus occurred.

The median maternal saline-agglutinin titre during the first week after delivery in this series was one dilution higher than that encountered in our prospective study of heterospecific pregnancies. Further, in a slightly higher proportion than in the latter group, the maternal anti-A agglutinin titre in albumin at 37°C exceeded that in saline at room temperature by at least two dilutions. This is taken to indicate a form of immune response in agglutination.

Hemolysins against adult A₁ cells were demonstrated in 35 out of 36 maternal sera, but were of little diagnostic aid as they were equally common in our ordinary heterospecific series. Hemolysins against infants' A cells were demonstrated in 17 out of 19 maternal sera, but proved hardly more helpful. After neutralization of saline-agglutinin by A or B group specific sub-

stance the maternal sera gave a positive indirect antiglobulin test in 26 out of 36 cases and residual agglutination of such cells in albumin in 19 out of 36 cases. The former test appeared practically more useful. Both reactions were somewhat more often positive in these mothers of affected infants than in the ordinary heterospecific pregnancies studied previously.

Partly because of the manner in which they had been selected, the infants always gave a positive indirect antiglobulin test against adult cells of their own group. The presence of an incompatible agglutinin acting in an albumin medium was also demonstrated in 15 out of 21 infants' sera. This test appeared less useful and technically satisfactory than the indirect antiglobulin procedure.

The direct antiglobulin test performed with commercial antiglobulin serum was positive in 13 of the 35 infants tested, whereas the test performed with titrated native absorbed antiglobulin serum proved positive in 24 of 27 cases at a dilution of 1:100. It was also shown that the result was likely to be negative after the first day when commercial serum was used and only after the third day with the titration method.

These results are discussed in relation to the findings of other workers.

Children of Alcoholic Fathers

by INGVAR NYLANDER

(*Supplement 121*)

A large number of the children admitted to the Department of Child Psychiatry at the Kronprinsessan Lovisas Barnsjukhus, Stockholm, were the children of chronic alcoholics. The frequency of divorce in the families of these children was remarkably high. The commonest cause of the child's being admitted for investigation was anti-social symptoms of different kinds, such as adaptation difficulties in school, truancy, pilfering, running away, stealing, sexual instability, etc. The preliminary investigation showed that mental disorders were more common among boys from broken homes than among boys from intact homes. On the other hand, no corresponding difference between the groups of girls was found. In addition, it was shown that adaptation difficulties were more common among boys than among girls. It would therefore be expected that there were more boys than girls in the clinic material. Such was, indeed, the case.

In many cases, the symptom picture presented by these children is difficult to interpret, because it is dominated by physical symptoms. The latter, which appear more commonly among girls than among boys, often result in extensive, time-consuming and unnecessary investigations.

The clinical investigation seldom leads one to the father's alcoholism. Since the children's parents, in addition, co-operate badly throughout in many cases, the fact of father's alcoholism has remained obscure during the whole time that the children have been in hospital. In this way, the clinical investigation has been incomplete and the treatment of the child inadequate.

One of the causes of the poor co-operation of the parents, has probably been that the alcoholic father lacked insight into the illness or felt himself incapable of giving up his alcoholic habits. In addition, the wife clearly backed him up, often because of fear of reprisals if she should give him away. In favour of the latter was the fact that children who were brought to the hospital, because of general symptoms of nervousness, almost always came from divorced homes, where the mother looked after the child alone.

Because of the above, a check must always be made during child-psychiatric investigation in Sweden with the Temperance Board's register, to see whether the child's parents are registered there as alcoholics. However not all alcoholic parents will be discovered, even by this means. In both the subject series in Part I and in the clinic material, about one third

of the alcoholic fathers were not registered with the Temperance Board. In such cases, the mental symptom-picture in the children can be of great help in revealing very bad home conditions, including alcoholism. Intensive, prolonged and treatment-resistant symptoms, such as head-

ache, abdominal pain, general tiredness, attacks of different kinds, disorders in walking, etc., should always arouse suspicions of severe disturbances in the home, if the physical examination has given no explanation of their cause.

Problems and Progress of Neonatal Paediatrics

Symposium, July 21, 1959 at the IX International Congress of Paediatrics at Montreal

Chairman: CLEMENT A. SMITH, Boston

(Supplement 122)

1. Anaerobic Metabolism and Neonatal Existence and Survival. *C. A. Villee, Boston.*
2. Biochemical Aspects of Birth, Anoxia and Resuscitation. *L. S. James, New York.*
3. Physiological Aspects of Temperature and Oxygen Effects on Newborn Infants. *P. Karlberg, Stockholm.*
4. Changes in the Circulation and Lungs at Birth. *J. Lind, Stockholm.*

1. Previous work demonstrated the great ability of the fetal and newborn mammal to withstand severe hypoxia; this ability was shown to be independent of the cytochrome system while greatly affected when the glycolytic cycle is inhibiting. The energy yield of the anaerobic decomposition of glucose to pyruvate is small (2 energy-rich P-compounds per molecule glucose) in comparison with the oxidation of pyruvate to CO_2 and H_2O (18 energy-rich P-compounds per 1 molecule pyruvate). The

present author studied enzymatic activities of fetal and newborn tissue (rats and humans) under aerobic and anaerobic conditions. He found that the glycolytic rate of fetal and newborn tissue under aerobic conditions in vitro (and probably also in vivo) is slightly higher than that of adult tissue. This difference is much more pronounced under anaerobic conditions. The enzymatic activities of fetal tissue were only slightly damaged by one hour of complete anoxia, while two hours of anoxia produced more severe damage. The author concludes that a prolonged period of tissue hypoxia towards the end of the pregnancy leads to an accumulation of substrates of the glycolytic cycle. This in turn brings about an adaptive increase in the enzymatic activity of these and, perhaps, also other energy-yielding anaerobic reactions, thus providing an increased ability to withstand severe hypoxia. Lipogenesis does not contribute to this ability, since it

yields no energy. Under anaerobic conditions its rate decreases to one tenth the aerobic rate.

2. The author studied the changes of oxygen saturation, buffer base, pH, $p\text{CO}_2$ and potassium levels in the umbilical artery of vigorous and depressed newborn during the first hour of life. He found that the oxygen saturation immediately after birth varied between 0-70 % in vigorous and 0-20 % in depressed infants, thus demonstrating the extreme lability of oxygen levels. With the onset of respiration an almost immediate recovery of the oxygen saturation took place. On the other hand, the measurements of buffer base, pH, $p\text{CO}_2$ and potassium levels showed a severe acidosis in all depressed infants. A further increase of the acidosis occurred during the first minutes following delivery. Thereafter a slow recovery took place within the first hour of life. Similar changes—yet less pronounced—occurred in the vigorous group. Medication of the mother as well as unusual delivery trauma resulted in a reduction of the recovery rate. Oxygen breathing of the mother had no effect on the metabolic values of the baby. It is concluded that the oxygen saturation levels in umbilical blood are not representative for the true intrauterine environment of the fetus and that the common belief of intrauterine hypoxia towards the end of the pregnancy must be reviewed. Furthermore, it seems that the degree of acidosis is a better indicator of any oxygen deprivation during delivery than the actual oxygen saturation level. In caring for newborns, it must be born in mind how quickly the pH can fall with severe hypoxia.

3. Several investigations have shown that the heat regulation in newborn infants as well as in premature infants is essentially the same as in adults. The well-known instability of the temperature of the newborn, therefore, may be mainly due to the fact that the relationship between body surface and body mass is $2\frac{1}{2}$ - $3\frac{1}{2}$ times greater in newborns than in adults. Another important factor in temperature regulation is the oxygen tension of the tissue. It is believed that the oxygen tension of the fetal tissue is significantly lower than in adult tissue and that a pronounced increase will take place with the onset of respiration after birth. This increase, while innoxious for normal infants, might produce some difficulties for infants which have been subject to severe hypoxia, since increased oxygen levels in the breathing air are responsible for vascular reactions (retrolental fibroplasia) as well as disturbance of lung function. Therefore, it may be reasonable to keep premature infants in an atmosphere of 15 % oxygen—perhaps combined with mild hypothermia. Under these conditions, the oxygen consumption of the tissue will be significantly lowered. While hypothermia alone has been shown to afford some protection against damage from severe hypoxia, it was of no avail when employed routinely on premature babies during the neonatal period.

4. For the neonatal adaptation to extrauterine life, respiratory and circulatory functions are intimately connected. In the foetus, the lungs are not aerated, the pulmonary resistance is high and the pulmonary blood flow low. Thus, the ductus arteriosus acts as a bypass for the blood

around the "sleeping" lungs. The comparatively well oxygenated blood coming from the placenta is to a significant extent directed to the brain via the ductus venosus and the foramen ovale. At birth, the lungs are aerated: the major factor in the lung expansion is the active inflation under negative pressure. This event acts as a focal point around which many of the changes in the circulation occur. The resistance in the pulmonary circuit drops, the pressure in the pulmonary artery falls and the pulmonary flow increases. The increased pulmonary venous return to the left atrium raises the pressure above that of the right atrium and the valve of the foramen ovale

closes more or less completely. These are rapid changes and normally occur within a few minutes of birth.

The normal lung function, after a "kicking" start immediately following birth, adjusts itself to the environment during the first few hours of life.

The neonatal circulation is characterized by a right ventricular and pulmonary arterial hypertension of moderate degree, a patent ductus arteriosus with a left to right shunt at rest, and a functionally closed foramen ovale. Adjustments gradually occur over a period of several days to the adult type of circulation.

Jean-Claude Vuille, Uppsala

Radiography Studies of Respiration in Infants

by JAMES F. BOSMA, YASUAKI TAKAGI and JOHN LIND

Supplement 123

Part I. Disability of Oral Function in an infant Associated with Displacement of the Tongue

Report of an infant who had disability of feeding and other oral function similar to that observed in those having hypoplasia of the tongue and/or palate. But in this subject these structures were of normal size, form, and motion. It was inferred that disability in this subject was due to inhibition of these oral performances incident to abnormalities of cervical postural mechanism.

It is proposed that normal suckle can be performed only against a background of regional inhibition of the musculature

accomplishing antereflexion of head and neck.

The particular clinical problems of this infant were relieved by a novel technique of prone position feeding.

Part II. Glossopharyngeal Respiration as a Part of Focal Seizures of the Pharyngeal Area in an Infant

The rare and distinctive motor performance of glossopharyngeal respiration (GPR) is reported as a part of seizure manifestation in an infant one month of age. This GPR is essentially identical with that learned spontaneously or by intention in some poliomyelitis patients having severe respiratory paralysis. It has also

been observed as an isolated performance in the respiratory transition at the moment of birth. It is inferred that this is a mechanism or performance which the subject has potentially but does not otherwise employ.

Part III. Roentgenologic Observations of Motions of the Upper Airway Associated with Establishment of Respiration in the Newborn Infant

The whole of the respiratory organization is involved in the initial aeration of the lung and establishment of the respiration.

The pharynx region may perform dis-

tinctively at this time in an engulfing action (glossopharyngeal respiration), the motions of which are highly similar to those of ingestion of bolus into the esophagus.

The more familiar respiratory modulations of the upper airway are also in action at this time, performing in relation to a comparatively stable hyoid base. These respiration-patterned motions may result in closure of the whole of the pharynx or the larynx.

The mechanisms of elicitation of these varied actions of the upper airway, their immediate motor mechanisms, and their effect upon pulmonary ventilation require further investigation.

PROCEEDINGS OF PEDIATRIC SOCIETIES

Finnish Pediatric Association

Meeting February 14, 1959

J. H. P. Jonxis (The Netherlands): Some Investigations on Rickets.

DISCUSSION.—*C.-E. Riih :* The close relationships between the metabolisms of phosphorus and calcium are well known. What is your personal opinion as to the action of vitamin D, does it primarily exert its influence on the calcium or on the phosphorus? — *Jonxis:* I do not know it for certain. I believe it has a direct influence on the retention of aminoacids in the kidney and on the absorption of the calcium from the intestine. — *H. Kalliala:* Do you think there is a difference between the vitamin D in fish liver oils and in concentrates? I have had

the impression that smaller amounts of vitamin D in cod liver oil will suffice to prevent rickets than do those given in concentrates.

— *Jonxis:* I do not think there is a difference in regard to vitamin D. I should, however, prefer fish liver oils because of their content of vitamin A and unsaturated fatty acids which are otherwise scarce in our foods. — *N. Hallman:* Have you seen many cases of hypercalcemia in Holland? — *Jonxis:* Only very few ones. The reason for this is, in my opinion, the smaller amount of alkaline foods in the diet of our children compared with that in England where hypercalcaemia has been encountered much more often.

Meeting April 24, 1959

Piero Foa (USA): Glucagon.

DISCUSSION.—*Zaida Eriksson-L hr:* In studies of the function of the suprarenal cortex in allergy performed at the Hospital for Allergic Diseases in Helsinki we have paid special attention to the carbohydrate metabolism which to a great extent is influenced by the steroid hormones. In 75 % of the about 400 allergic cases studied a prolonged and increased fall of the glucose tolerance curve was seen compared to the normal. In 15 % the blood sugar did not reach its initial value within 6 hours. Increased sensitivity to insulin was also observed. The insulin tolerance showed in 75 % of the cases a latency time of less than 6 min. In 15 % it was less than 3 min. The decrease was rapid and reached mostly

hypoglycemic values of 25–40 mg %. Hypoglycemic symptoms were often seen, sometimes also unconsciousness and cramps. The intravenous glucose tolerance test showed within 90 minutes no peripheral uptake of the glucose. Through courtesy of the Lilly Laboratories we have had the opportunity to investigate the influence of glucagon, the new hyperglycemic-glycogenolytic hormone from the α -cells of the pancreas. Studies were performed on 30 allergic patients, mostly children. Glucagon was administered i.v. 1.4 ml/m² body surface.

The following results were obtained in our studies:

- 1) Glucagon tolerance test—blood sugar curve normal

- 2) Insulin-glucagon tolerance test—increase of blood sugar instead of decrease
- 3) Comparison of arterial and venous blood sugar values
 - a) after i.v. glucagon-peripheral utilization excellent
 - b) after i.v. insulin-glucagon-peripheral utilization excellent
 - c) after i.v. glucose-glucagon-peripheral utilization better than with glucose alone
 - d) after i.v. insulin-glucagon-glucose-peripheral utilization very good

Three severe cases of asthma in children were treated with glucagon for 2-3 months. This treatment diminished markedly the asthma attacks and made them happy and alert. — *Foa* expressed his interest in these studies. Remarkable was the poor peripheral utilization of glucose in these allergic children which was entirely normalized by the adding of glucagon.

Sven Kræpelien (Sweden): Some Aspects on the Prognosis of Childhood Asthma on the Basis of Respiratory Studies.

DISCUSSION.—*C.-E. Råihä*: Can you tell me your opinion as to where the resistance to respiration in asthma is located, whether in the bronchi or in the bronchioli. — *Kræpelien*: That is not known exactly, it is thought to be in the bronchioli. — *O. Pettay*: I should like to recommend the use of spirometry in following the progress of asthmatic children, especially the duration of expiration gives valuable clues to the state of the disease. The necessary apparatus is very simple and a home-made spirometer as the one I use does serve its purpose very well. — *P.-E. Heikel*: Is it possible to measure the respiratory volume by simultaneous frontal and lateral radiography of the chest? — *Kræpelien*: Only rather rough measurements can be made by that method and in these cases it is just small differences in volume that are important. Such a roentgenological study is, however, in progress at the Karolinska Hospital in Stockholm.

Meeting November 14, 1959

Forrest Adams (Los Angeles, USA): Pulmonary Hypertension in Congenital Heart Disease.

Approximately one per cent of all children born alive have congenital heart disease. Many of these children do not live beyond the first two or three years and those that do live eventually develop complications which cause death, particularly in those patients who have shunting of blood from the left side of the heart to the right side. They are prone to develop pulmonary hypertension. In the case of patients with ventricular septal defect this is a serious complicating factor in the small child. Even though the surgeons, technically, are able to close the defect in the heart the end results of the pulmonary hypertension preclude the possibility of successful surgery. The pulmonary hypertension, if allowed to exist long enough,

creates a scar tissue or sclerosis of the pulmonary arteries. A report is given on some studies performed in the laboratories at the University of California at Los Angeles Hospital. These studies consisted of performing a right heart catheterization followed by injection of a drug, acetylcholine, through the catheter into the heart and then measuring the response of the patient to this drug. The response was measured by recording the pressure in the pulmonary artery and in the systemic arteries over a short period of time. It was found that those patients who had a good response to the drug were those patients who also were able to benefit by surgery. Those patients who failed to respond to the drug were not benefited by surgery. Eighty children were studied in this fashion and, in general, it was found that those patients who failed to respond to acetylcholine were over six years

of age. As a result of these studies, it is felt that this test is very useful in determining whether or not a patient can benefit by surgery for his congenital heart lesion. The importance of early heart surgery to prevent the irreversible changes in the lungs due to the shunting of blood from the left side to the right is stressed. In our experience the risks of surgery are far less than the risk of medical management without surgical treatment. The surgical risk at the present time is approximately ten per cent. The chance of living beyond two years of age is less than twenty-five per cent. Eventually techniques for diagnosis and treatment will be developed to the extent that surgery can be performed in the very early infancy period, prior to six months of age.

James Bosma (Salt Lake City, USA): Motions of the Pharyngeal Region with Initial Inflation of the Lung of the Newborn Infant.

A report is given on observations obtained from twenty-three infants by lateral roentgenograms taken at intervals of half, one third or one sixth of a second using a Schönander rapid x-ray film changer. These studies have demonstrated a coincident activity of the pharyngeal, oral and laryngeal area with initiation of respiration. This activity was seen in various patterns and on various schedules and sequences. In general the pharyngeal region was more active than the thorax and active prior to and on a more rapid schedule than the thorax. This activity in the pharyngeal region in some infants was in an air swallowing pattern, essentially identical to the usual form of respiration in amphibians, hence called "frogbreathing". This form of respiration has also been observed in an infant having pharyngeal disorder, and repetitive glosso-pharyngeal "frogbreathing". It is the usual manner of respiration in some persons who have poliomyelitic paralysis of the thorax so that they cannot breathe in the usual manner. Other infants at birth simply accomplished a closure or squeezing shut of the pharyngeal

region in a variety of patterns. The contribution of these pharyngeal motions to the accomplishment of the first respiration and full aeration of the lungs at birth is not clear but is under continuing study.

John Lind (Stockholm): Functional Adaptation after Birth.

J. Lind, T. Peltonen, L. Törnwall, and C. Wegelius (Stockholm, Turku): Roentgencinematographic Studies on the Aeration of the Lung at Birth.

An Arriflex 35-mm movie camera connected with a Philips image intensifier has been used to record the roentgenological status of the thorax of the human baby at the very first moments after birth. The initial aeration takes place in peripheral areas of the lung. The final aeration follows after varying periods of time and the residual air content varies in different individuals. In side view the filling of the upper airways up to the bronchi is seen. The changes in the heart volume are noticeably independent of the respiratory movements.

L. Hirvonen, S. Jäykkä, T. Peltonen and L. Rauramo (Turku): The Changes in the Foetal Circulation at Birth.

Roentgencinematographic recordings have been performed with an Arriflex 35-mm movie camera connected with a Philips image intensifier on foetal lambs catheterized in utero for the introduction of radiopaque material into the jugular or femoral vein or the umbilical artery. The exposure rate was 24 per second. When radiopaque material is injected into the jugular vein prior to the first breath, the aorta fills periodically through the arterial ductus from the right heart. In retrograde aortagraphy the pulmonary artery does not fill from the aorta. After the first breathe there is no evidence of flow through the arterial ductus. When the injection is performed into the femoral vein prior to the first breathe, approxi-

mately two thirds of the contrast material flows through the foramen ovale and one third into the right atrium. The clamping of the umbilical cord and the initiation of respiration did not change noticeably the pulsatory flow in the caval vein and flow of dye through the foramen ovale to the left atrium.

DISCUSSION.—*C.-E. Riih  *: First of all I wish to extend my congratulations to those concerned with the presentation of these new and valuable experimental results which we have had the opportunity to see and hear. As I have been interested for many years in foetal and neonatal metabolism I ask myself the question: Do the circulation and respiration serve metabolism or the metabolism the circulation and respiration? The essential thing is that it is a mutually reciprocal action. As far as we know the production of heat and the oxidation associated therewith is about 1 Cal/kg/hour during foetal life and on delivery the value is lower. Immediately after birth when breathing has begun, the production of heat is about 2 Cal/kg/hour. This rapid rise indicates the disappearance of a factor which depresses the metabolism. It is known that the CO_2 -tension in the foetus is higher than in the mother and also higher than in the healthy newborn child. In *in vitro* studies on the metabolism of human blood N. R  ih   & O. Forsander have found a correlation between the age of the blood donor and the appearance of inorganic phosphate in the incubation medium per unit time. Further they have found that an increase in the CO_2 -tension of the incubated blood produces a decrease of the glucose consumption by foetal and cord blood more strongly than of adult blood. Simultaneously an increase of the CO_2 -tension can be noted in the Warburg flasks despite the decreased glucose consumption. This could be explained by an increase in the activity of the phosphogluconate oxidative pathway, at the expense of glycolysis. The results are consistent with the fact that the production of lactic acid from glucose is strongly inhibited by

decreasing pH (Rummel, Pfl  ger & Seifen, *Biochem Zschr* 330: 310, 1958). These observations, made *in vitro*, lead us to the studies by Cross, Tizard & Trythall, published in *Acta P  diat* 47: 217, 1958. Their work indicates that when a full-term newborn infant increases its respiratory minute-volume, the consumption of oxygen rises. If a premature baby is transferred from air to an atmosphere which contains 15 % oxygen, the baby's consumption of oxygen drops to a greater extent if the respiratory minute volume is decreased and less if the minute volume is increased. In full-term newborns, on the other hand, when transferred from air to 15 % oxygen, the drop in the consumption of oxygen is not dependent on the minute volume of the respiration. If one correlates from the above research report the change in the respiratory minute volume with the content of CO_2 in the exhaled air, as we have done, it is found that with an increase in the respiratory minute volume by about 10 %, the CO_2 content of the exhaled air in the premature series, and in the series where full-term infants in both periods of investigation breathe air, decreases by 5-10 %. When the full-term infants are transferred from air to a 15 % oxygen atmosphere the CO_2 content in exhaled air decreases by about 20 % by a 10 % increase in the minute volume. This considerable decrease of the CO_2 content in the exhaled air is probably due to a reduction in the depth of breathing, although the minute volume is increased by the increased frequency of respiratory movements. This superficial breathing would result in an increased alveolar CO_2 -tension as well as a consequent impeding of the consumption of oxygen. In an earlier work Cross showed that full-term babies react just in this way on transfer from air to 15 % oxygen, whereas prematures primarily increase the depth of breathing in corresponding situations and are thus able to better breathe out their CO_2 . It would not be surprising to find that variations in the CO_2 -tension would have an effect upon circulation, even though metabolism in animal experiments appears to

react more sensitively to variations of CO_2 , than respiration and circulation do. (Rein & Otto, *Pflügers Arch Physiol* 243:304, 1940.) It would be worth while to try to examine the effect of decreasing CO_2 -tension upon the functional closure of the ductus arteriosus and of increasing CO_2 -tension upon the reo-

pening of this shunt. According to this reasoning, a placental sufficiency of CO_2 elimination would be a decisive regulator of the oxygen consumption of the foetus and further for the normal freeing of respiration and the change of circulation at birth.

Meeting December 12, 1959

M. Kaila (Helsinki): The Influence of the Environment on the Sick Child.

DISCUSSION.—*O. Somersalo*: Do early frustrations always result in unfavourable development? Is it not possible for them sometimes to produce useful aggressions—pioneer spirits?—Do you regard soiling always as psychogenic in origin? We see cases in which obstipation of long standing seems to be the reason and who stop soiling after the obstipation is treated. — *M. Kaila*: People who do not acquire the ability to master their frustrations cannot develop into mature individuals. The child must be helped to accept unavoidable frustrations so that he will not accumulate aggressions.—The cases of soiling which I have seen have all been of psychogenic origin. — *N. Hallman*: Pediatricians certainly also see cases of soiling on a non-psychogenic basis, e.g. those with an anal fissure, who rapidly respond to treatment of the fissure. — *H. Kalliala*: I should like to point out the fact that home-care is not always preferable to institutional care. If a home is a broken one or the mother is working outside the home then an institution of high standards with suitable

mother substitutes may be the better place for a child. — *M. Kaila*: Large statistics clearly show the unfavourable effects of institutional care, there are, of course, exceptions to this general rule. Small institutions are to be preferred to big ones. The lack of the father figure can usually not be compensated for in institutions. — *C.-E. Riih  *: Could it be possible that the lack of memory about events before the age of five years is due to the relative scarcity of connections between ganglion cells of the brain up to that age? — *M. Kaila*: Possibly, we do not know much about this. — *T. Araj  rvi*: Referring to what Dr. Kalliala said I should like to emphasize the fact that a satisfactory mother—child relationship does not depend so much on the amount of hours a mother is able to spend with her child but on the quality of that relationship. — *H. Huhtikangas*: It is important to find out ways by which young parents can be properly informed about the importance of these things, so far those who are in greatest need of information on these aspects of child care do not realize it themselves and do not ask for advice.

Niilo Hallman, Helsingfors

Swedish Pediatric Society

Meetings Dec. 4-5, 1959

Gunnar Brante, Kurt Kaijser and Anna-greta Malmström-Groth: Aids in the Diagnosis of Gargoylism.

An essential part of the metabolic alterations in gargoylism consists of an excess of acid mucopolysaccharides in the form of chondroitin sulphate B and heparitin-sulphate, at least partly in a protein unbound form. These mucopolysaccharides give a metachromatic reaction with basic thiazole dyes, i.e. toluidine blue, which reaction may be used as a convenient way of demonstrating their occurrence. The diagnosis of gargoylism is usually easy to establish, when its typical symptoms are apparent. On the other hand, the diagnosis may be doubtful in newborns or young children, and even at a later stage it may be difficult to distinguish, for example, from Morquio's disease. In such cases it is desirable to have access to some simple laboratory methods. We have attempted to adapt the metachromatic reactions to show the metabolic alterations. Four children with gargoylism have been examined during life with different tests. Case 1 a girl 7 years of age, had marked clinical changes. Cases 2 and 3, twins, a boy and girl 2 years of age, had even more marked changes. An older sister had died of gargoylism and another sister, Case 4, 1 year of age, had begun to show signs of the disease. The following examinations were carried out: *Easily accessible body fluids and secretions.* No definite pathologic metachromasia was seen in the nasal secretions, tears, or gastric juice. In the saliva, pathologic metachromasia was sometimes suggested. *Urine.* As little as one drop of a 24 hour urine sample

dried on filter paper, often showed rather marked metachromasia. Alcohol precipitation of a certain amount of 24 hour urine which was then dissolved in $\frac{1}{10}$ volume of water and thereby concentrated, showed very marked metachromasia. In normals there was no, or at most only a suggestion of, such a reaction. *Cerebrospinal fluid.* In the sediment from the liquor cells filled with metachromatic staining substance were found. *Biopsy* material from liver, obtained by subcutaneous puncture, and from punch skin biopsy was examined for the occurrence of metachromatic staining substance. Squashed tissue, pressed and dried on filter paper, showed metachromatic staining. On chromatographic and electrophoretic examination a rapidly running substance was demonstrated in the tissue. The metachromatic staining substance was completely free of more slowly moving protein. In alcohol fixed tissue from the liver metachromasia was shown in the kupfer cells and in some of the epithelial cells. In the skin there was evident metachromasia in probably fibrocytes primarily of the papillary layer and among the hair follicles. The condition that the water soluble mucopolysaccharides do not separate from the tissue in preparation lays in the fact that the alcohol used in the histological technique was never less than 70 %.

G. Christiansson, K. Ekengren, Y. Larsson and G. Sterky: Prognosis in Juvenile Diabetes.

The incidence of vascular sequelae was estimated in a series of 169 cases of juvenile diabetes treated with a liberal diet. Onset of

the disease was prior to 1943 and age at onset less than 16 years. The total mortality in the series was 24.9 %, the half of which was caused by diabetic angiopathy. In most cases the cause of death was renal insufficiency. The cumulative mortality in angiopathy rose continually with the duration of diabetes. However, after a duration of 25 years no further increase was observed. Among the survivors, diabetic retinopathy was apparent in 78 %. Vascular calcifications in the lower extremities were shown in the same percentage, whereas diabetic nephropathy was present in 39 % only. In these figures are also included cases with minimal lesions who had no subjective symptoms. Full working ability was present in 80 %. The frequency of angiopathy showed some correlation to the duration of the disease. However, this was less evident than in other similar studies. Especially notable was the fact that the frequency of nephropathy declined in those patients who had had diabetes for more than 22 years. As the same group of patients had been examined in a similar way 10 years earlier (Larsson *et al.*, *Diabetes* 1: 449, 1952), the course of the disease, especially the retinopathy, could be studied. This showed that a good $\frac{1}{4}$ of the cases, contrary to expectation, had not worsened during the 10 year period in question. Blood cholesterol levels were correlated to the duration of the disease. Cases with advanced angiopathy had at examination 10 years earlier had a higher cholesterol level than those with no or minimal changes. The patients' dietary habits, showed a considerable individual variation, and caloric overconsumption was usual. Obesity, however, was rare. The prognosis in this series of juvenile diabetics with onset of illness prior to 1943 was thus in some respects very poor. More intensive control of the disease and continued research into possibilities of early diagnosis and prophylaxis of diabetic angiopathy may lead to better results. For this, however, it seems important that, wherever necessary, centres for treatment of diabetes be strengthened as regards staff, equipment and laboratory assets.

K. Kaijser: It seems to me that with respect to treatment, diabetic children can be divided into two main groups. The one group is easy to control with a definite insulin requirement, can have the same requirement for a long period of time, shows small variations in blood sugar, and seldom has acetonuria. The second group must repeatedly be admitted to hospital for control, and is difficult to adjust to an insulin dosage. These children are easily in a pre-comatous stage and often have recurrent acetonuria. My question is: Can one from the present well investigated diabetic series draw any correlation between the difficulty to treat labile cases, and the occurrence of an increased number of developing retinopathy, nephropathy, or similar complications. Or is this risk the same as that for patients who appear to be easy to treat.

Ake Lundberg: Prognosis in Paroxysmal Atrial Tachycardia and Atrial Flutter in Infancy.

The case material consists of 39 infants. Thirty-three showed paroxysmal atrial tachycardia and 6 atrial flutter, all diagnosed electrocardiographically during an attack. Eighty per cent started prior to the age of 2 months, the majority of the flutter cases appearing in the neonatal period. Five of the 6 children with flutter had only one episode, whereas 82 % of those with paroxysmal tachycardia had recurrences. All the flutter cases and 68 % of those with paroxysmal tachycardia were free of attacks after 4 months of age. Of the latter 6 % had attacks after 2 years of age. There were no deaths among those with flutter. The combination of congenital heart disease and paroxysmal tachycardia carries a poor prognosis. The mortality among those with paroxysmal tachycardia without evidence of organic heart disease was 6 %. The follow-up period exceeded 1 year in all cases. In 8 of them it was between 5 and 14 years. All the children were within the normal limits for height and weight. There was no evidence of organic heart disease on physical

examination and X-ray examination was normal. Electrocardiograms showed an increased sensitivity of the atrial conduction system in the form of incomplete sinoauricular block and/or ectopic activity in $\frac{1}{3}$ of the cases. Pre-excitation waves occurred at some time in 33 % of the children with paroxysmal tachycardia, in whom it was twice as common in those who presented attacks after early infancy. The children often showed remarkably neurolabile features. (Detailed publication at a later date.)

T. Ehrenpreis, N. O. Ericsson, L. Billing, R. Lagercrantz, U. Rudhe, and J. Winberg:
The Surgical Treatment of Ulcerative Colitis in Children.

The effectiveness of the medical treatment of ulcerative colitis has improved in the last decade. In spite of this the results in the long term prognosis is often unsatisfactory. In severe cases the child's general condition and indeed his whole way of life may be severely affected, and his physical and psychic growth and development will suffer. With severe, long standing disease there is also a considerable risk of malignant com-

plications (carcinoma of the colon). In view of these facts we have broadened our indications for surgery in the treatment of ulcerative colitis in children. At the Pediatric Clinic of Karolinska sjukhuset we have now operated on 19 patients. The indication for surgery was, in most of the cases, long standing debilitating disease. In all cases colectomy has been carried out. In 10 cases an ileostomy was constructed and in three of these the rectum was removed. In the remaining nine cases with less severe rectal changes ileorectal anastomosis was performed. The results have been good. All the patients survived surgery and have shown a good improvement afterwards. Seventeen patients have been observed one to two years after surgery. Those with an ileostomy have, to a great extent, adjusted themselves as well as those with an ileorectal anastomosis. In only two cases has the rectum healed after operation but untill now we have not had to resort to secondary ileostomy in those treated by anastomosis. The patients often show a marked psychic immaturity and insecurity, particularly as regards emotional development. Earlier operation would perhaps have allowed a more normal psychic development.

BOOK REVIEWS

Kjellberg, S. R., Mannheimer, E., Rudhe, U. and Jonsson, B.: Diagnosis of congenital heart disease.

The Year Book Publishers, Chicago. 866 p., 727 fig., 2nd edition 1959.

The first edition of the well-known work of Kjellberg and collaborators which was reviewed in this periodical a few years ago (*Acta paediat.* 44:596, 1955) has long been out of print. For several reasons the authors have not wanted to get it merely reprinted. The case material on which the work is based has in the meantime almost doubled, i.e. from 396 to 742. Application of new methods of examination and modification of the earlier ones has made it possible to make further differentiations in certain types of malformations and to arrive at a more precise diagnosis in some of the cases. Furthermore, the correctness of the diagnosis could be definitely proved in an increasing number at operation. This new edition has, naturally, become more extensive but not at the cost of lucidity. The increase in size is chiefly due to the addition of new figures, especially angiocardiograms which are of the same good quality as the previous ones. All chapters are thoroughly revised and some parts have been rewritten and/or extended. The classification of atrial septal defects and abnormal pulmonary venous return has been made more precise than in the first edition. The etiology of pulmonary hypertension in left-to-right shunts and its relation to age is discussed in more detail. The physical working capacity has been examined in a number of patients with some of the more common types of malformations and has been correlated to such parameters as pressures and flows. In addition, hemodynamics at rest and at work have been studied in a few adults who are otherwise not included

in the material. Four entirely new chapters are added, the most important of which deals with corrected transposition. The advances in cardiology during the past few years are reflected in the number of references which has increased to about double. This work, having now been extended and brought fully up to date, remains one of the most outstanding in this field and is warmly recommended to all who are interested in congenital heart disease.

Lars-Erik Carlgren, Göteborg

Herman G. Wolf: Röntgendiagnostik beim Neugeborenen und Säugling.

570 ill. 317 pages. Wilhelm Maudrich Verlag, Wien-Bonn-Bern, 1959. Price 98 DM.

This book gives an account of the main roentgenological findings of the skeleton, thorax and abdominal organs of neonatals and infants. A concise description of the clinical background is added to the roentgenological data. Much space has been saved by omitting all kinds of references in the text. These have instead been collected in groups after each main section. The references comprise no less than 1500 numbers and are to be considered as highly representative of the pertaining European and American literature. The illustrations, which are abundant, are almost without exception of high standard. They appear close to the appropriate text and it is obvious that the author has devoted much meticulous work to the selection of most illustrative cases. The skeletal system has intentionally been compressed mainly to deal with the common lesions because of the fact that Swoboda, of the same clinic, recently has issued a separate treatise on that topic. A Scandinavian reader nevertheless is impressed by the richness of il-

illustrations devoted to syphilis of the bone, a disease which is rare in Northern Europe. Too little attention has, on the other hand, been paid to modern techniques and view points in exploration of the urinary tract and the circulatory system. These objections do not, however, essentially reduce the general value of this new contribution to an important field of roentgen diagnostics. This work is to be recommended both to roentgenologists and to pediatricians.

Ulf Rudhe

Dringliche Chirurgie beim Säugling und Kind. By H. E. Grewe.

180 pages. 60 illustrations. Price DM 25.—.

In the last few decades the field of children's surgery has been extensively developed and a considerable number of textbooks have been published on the subject. Now, Grewe, presents in brief summary form the acute surgery of neonates and children, based mainly on his personal experiences from surgical clinics in Berlin and Düsseldorf. Emphasis has been placed on a diagrammatic presentation of the various diagnostic problems with simple drawings, showing the anatomy and the more frequently used operations. A schematic presentation of a field so rapidly progressing and where today such differences of opinion prevail, must certainly seem quite dogmatic to the reader. It will, however, be a handy pocket book for students and doctors confronted with the acute surgical problems of this age group.

G. Grotte, Uppsala

B. Levin, Helen M. M. Mackay, Catherine A. Neill, V. G. Oberholzer and T. P. Whitehead: Weight Gains, Serum Protein Levels, and Health of Breast Fed and Artificially Fed Infants.

Spec. Rep. Ser. med. Res. Coun. No. 296, London, 1959. 154 pages.

In this monograph there are 75 pages of text as well as an appendix of similar length

including figures, tables and references. This investigation is one in a series of studies of protein requirement at different ages. These were begun during the last war by "The Protein Requirement Committee"—a subdivision of the Medical Research Council. The original, more circumscribed, task was to determine standards for serum protein levels in full-term and premature infants. However, this presupposed continual clinical control in order to define a normal group of infants. Some of the resulting clinical data was analyzed in respect to weight increase, hemoglobin values, and—to a certain extent—frequency of infection and of rickets.

The material was made up of 946 infants which were investigated in connection with check-ups at a maternity hospital belonging to the Salvation Army. Of these infants, 744 appeared in the final study: 521 full-term and 223 premature. Some were breast-fed for quite a while. Others were bottle-fed with a roller processed dried milk preparation. For the full-term infants, type "full-cream sweetened milk" was administered; for the premature up to 1-3 months of age, type "half-cream" was administered. The observation period generally was the first twelve months. There were large individual differences in the frequency of check-ups.

A research group at Queen Elizabeth's Hospital for Children carried out the biochemical and statistical analyses. The material was gathered during 1947-50 while the study was only recently published—a reminder of the extensive work involved in completing study of this nature.

As was expected, a satisfactory increase in weight was found in both full-term and premature infants. This increase showed a tendency towards elimination of the initial difference in weight between the two groups during the first year of life. The method of feeding had no effect upon the weight curve of the full-term infants, but premature infants weighing less than 2000 g at birth showed a faster rise in weight during the 2nd to 8th week of life when bottle-fed. No difference in frequency of infection was noticed, but analysis was only made up to

the age of five months and no details of attendance, family structure, etc. are listed. Rickets was noticed only in a few cases: primarily in premature, breast-fed infants. The hemoglobin levels held acceptable averages. It should be noted here that all infants routinely received iron prophylaxis.

The relatively thorough serum protein analyses and fraction analyses are of special interest when used to compare the full-term and the premature infants. The difference in total serum protein at birth disappears by the end of the first year. The method of feeding did not affect this process. The examination of protein fractions verified the results of some earlier investigations. At the end of the second year of life, the gamma globulin levels were still lower than in adults.

It is interesting to compare the results in the present study in regard to full-term infants with similar material in the Norrbotten Study (O. Mellander, B. Vahlquist, T.

Mellbin and others, *Acta Pædiat* 1459: Suppl. 116). In this latter study, certain differences between breast- and bottle-fed infants appeared (see summary in *Acta Pædiat* 58: 619, 1959). When compared to breast-fed infants of 6-9 months of age, infants weaned early showed not only a somewhat quicker increase in weight but also a somewhat greater increase in length. At this time, the gamma globulin level showed a slightly higher value for bottle-fed infants. The number of acute infections during the first year of life was somewhat higher for bottle-fed infants, but the difference was not pronounced. A number of other investigations, including skeletal development, dental status, anti-body production and serum electrolytes, were only carried out in the Norrbotten Study and therefore no comparison of these results could be made.

Bo Vahlquist, Uppsala

ANNOUNCEMENT

The Tenth International Congress of Pediatrics

The Tenth International Congress of Pediatrics will be held in Lisboa, Sept. 9-15 1962. The Organization Committee has the following members: Prof. Dr. Carlos Salazar de Sousa, President, Dr. José dos Santos Bessa, Vice-President, Prof. Dr. Mário Cor-

deiro, Secretary General, Dr. Silva Nunes, Vice-Secretary-General. The address of the secretariat is Clinica Pediátrica Universitária, Hospital de Santa Maria, Avenida 28 de Maio, Lisboa 4.

The Fifth International Poliomyelitis Conference

The Fifth International Poliomyelitis Conference, sponsored by the International Poliomyelitis Congress and the Danish National Association for Infantile Paralysis and under the chairmanship of E. Juel Henningsen, will be held in Copenhagen, July 26-28, 1960. The Conference will deal with two subjects:

Part I Virology, and Part II Poliovirus Vaccines.

Correspondence and inquiries regarding the Conference should be addressed to the Secretariat of the Fifth International Poliomyelitis Conference, 5, Tuborgvej, Hellerup, Denmark. Telegraphic address: Poliocon.

From the Wenner-Gren Research Laboratory, Norrtull's Hospital and Södra Barnbörds-
huset, Stockholm, Sweden

Neonatal *T* Wave Patterns¹

by LEO STERN² and JOHN LIND

Introduction

In the study of the electrocardiogram of the newborn infant considerable interest has been shown in the behaviour of the *T* waves. Thus Ziegler (1), and Sodi-Pallares and co-workers (2), have described the changes occurring in *Tv*₁ within the first 24-48 hours of life, where the *T* wave changes from a positive to a negative deflection, to remain as such throughout infancy and childhood. They also discuss the simultaneously occurring change from slight negativity or isoelectricity to positivity of *Tv*₆.

As regards the *T* wave pattern in the extremity leads, little has been written of them beyond the notation that they are flattened and of low amplitude (3, 4). Indeed, Wenner & Doll (5), in writing about the variation in extremity lead *T* waves, excluded all infants under 21 days of age from their study on the grounds that such infants do not have *T* waves of any amplitude suitable for analysis.

In the course of an investigation into the electrocardiogram in the first few moments

of life (6), we have observed the presence of *T* waves of good amplitude in tracings taken before and after the first cry of the infant. These *T* waves, however, appeared to flatten out and in some instances to disappear entirely within minutes after birth. Because of this, an analysis of our material was undertaken and an effort to reproduce the phenomenon was made.

Material and Methods

The material consists of two groups of newborn infants. In the first group, designed as a longitudinal study of cardiovascular phenomena in the newborn infant, are included 32 newborns. These infants all had ECGs as well as X-rays and phonocardiograms taken twice within the first day of life and again on the 3rd and 6th day. The first ECG in this series was taken as early as 15 minutes after birth and repeated again at about 12 hours. Further tracings were then taken on the 3rd and 6th day.

Of this group totalling 32 infants, 18 infants were considered to have undergone a "normal" birth process and to have been mature infants both by date of delivery and by birth weight. "Normal" infants are taken as those requiring little or no effort at resuscitation other than routine suctioning, nor exhibiting any physical or physiological abnormalities in the immediate neo-natal

¹ Aided by grants from the Association for the Aid of Crippled Children, New York City.

² Medical Research Fellow, National Research Council, Canada.

period. All the infants in this group breathed and cried spontaneously within a few seconds after birth. There was no marked cyanosis in any of them, although most did exhibit the usually dusky extremities so common in newborn infants. The remaining 14 infants presented the following deviations from the "normal". Four infants had difficult deliveries, one because of a brow presentation and one because of a cord around the neck. Two of these were markedly cyanosed at birth. Two infants were considered to be abnormally large (over 5000 g), though not post-mature either by date or by appearance. Three infants were premature by both weight and gestational age, one of whom, one of a twin, died on the 4th day of life. One child presented the features of mongolism without any discernible cardiac pathology, and one child had the appearance of post-maturity combined with a deformed thorax. Finally, one infant had an elevated temperature at examination and two exhibited cyanotic attacks in the first few days of life which ceased spontaneously.

In all of these 32 infants delivery was by the vaginal route with no instrumentation, and a very minimal use of anaesthesia which was limited to a few drops of chloroform on a mask just as the head was crowning.

The observations concerning the behaviour of Tv_1 are based primarily on this first group of infants as is some of the supplementary information regarding the T waves in the limb leads.

The second group comprises 12 infants. Ten of these had the first ECG taken within 30 seconds after birth, of which seven yielded tracings prior to the first cry as well as immediately after. A follow-up tracing was then performed on each infant $\frac{1}{2}$ to 1 hour later.

All 10 of these infants were full term mature infants both by weight and dates, as well as clinical appearance. Six of these were classified as having undergone a "normal" birth process according to the previous definition, and showed no significant physical or physiologic abnormalities during the first week of life. The other 4 in-

fants were classified as "difficult" i.e. experiencing difficulty in the initiation of respiration. Of these, two were markedly cyanotic, one exhibited a picture of asphyxia pallida and one had difficulty with respiration following a cord around the neck presentation. All were successfully resuscitated, two requiring oxygen, and none showed any obvious ill effects on discharge from the nursery at approximately 6 days of age.

In the remaining two infants of the second group, who had tracings taken at 90 and 120 seconds after birth respectively, and who showed flattening of the T waves in the limb leads within $\frac{1}{2}$ hour after birth, adrenaline, 100 micrograms I.M. was administered in an attempt to reverse this phenomenon. The observations on the limb lead T waves are based primarily on this group.

As in the first group of infants all the babies in this group were delivered vaginally, without any instrumentation, and under the barest minimum, if any, of anaesthesia.

All recordings in both groups were made with an Elema 42 Mingograph 4 channel recorder at a speed of 50 mm/sec and a standardization of 1 millivolt = 10 mm. In the case of the infants in the second group, specially designed electrodes which could be applied manually to the areas of the anterior shoulder and groin were used in order to shorten the time necessary for the application of electrodes and thus permit the recording of a suitable tracing prior to the first cry of the infant.

Finally, in two infants the effect of the temperature on the T wave pattern in the limb and chest leads was observed, by obtaining simultaneous serial tracings and temperature measurements. An attempt to influence the changes by warming the infant by means of swaddling and hot water containers was also made.

Results

With respect to the question of the chest lead T waves and the behaviour of Tv_1 , our findings would confirm the

TABLE 1. *Time of first Observance of a Negative T Wave in Lead V₁.*

Case No.	Time negative T_{v_1} first observed	Comments
1.	48-72 hours	"normal"
2.	48-72 "	"normal"
3.	72-96 "	"normal"
4.	96 "	difficult delivery cyanotic at birth
5.	2 "	"normal"
6.	14 "	"normal"
7.	2 "	"normal"
8.	12 "	"normal"
9.	2 "	"normal"
10.	12½ "	"normal"
11.	10 "	"normal"
12.	12 "	"normal"
13.	12 "	"normal"
14.	48-72 "	"normal"
15.	4 "	"normal"
16.	1 "	"normal"
17.	21 "	"normal"
18.	23 "	difficult brow delivery
19.	30 minutes	"normal"
20.	21 hours	"normal"
21.	96 "	unexplained fever
22.	41 "	birth wt. 5000 g
23.	24 "	mongolism
24.	48-72 "	birth wt. 5200 g
25.	48 "	post-mature, deformed chest
26.	6 days	cyanotic spells
27.	17 hours	cyanotic spells
28.	30 minutes	premature
29.	12 hours	premature
30.	12 "	premature, died on 4th day
31.	34 "	asphyxiated at birth, cord around neck
32.	3½ "	cyanotic at birth, difficult delivery

previously described behaviour, i.e. that there occurs in the immediate post-natal period a change from a positive to a negative deflection of T_{v_1} , often accompanied by a change from isoelectricity to a positive deflection in T_{v_6} , and that this change appears to be independent of any changes in QRS, rate, rhythm, or any other obvious change in the format of the ECG. However, as is shown in Table 1, our findings would indicate that the time of occurrence

TABLE 2. *Changes in Standard Lead T Waves in the Immediate Post-Natal Period.*

T wave amplitudes are given in mm. — indicates T wave not practically measurable, i.e. less than 0.25 mm.

Case No.	Birth ECG	Time of follow-up	Follow-up ECG
33.	$T_1 + 0.5$ $T_2 + 2.0$ $T_3 + 1.25$	1 hour 15 min.	T_1 — $T_2 + 1.0$ $T_3 + 1.0$
34.	$T_1 + 2.0$ $T_2 + 3.0$ $T_3 + 2.0$	30 min.	$T_1 + 0.25$ $T_2 + 1.25$ $T_3 + 0.5$
35.	$T_1 + 1.0$ $T_2 + 2.0$ $T_3 + 1.5$	1 hour	T_1 — $T_2 + 0.25$ T_3 —
36.	$T_1 + 2.0$ $T_2 + 1.5$ T_3 —	1 hour	$T_1 + 0.5$ T_2 — T_3 —
37.	$T_1 + 3.0$ $T_2 + 1.5$ T_3 —	5 hours	$T_1 + 0.5$ T_2 — T_3 —
38.	$T_1 + 2.0$ $T_2 + 1.0$ $T_3 - 0.5$	1 hour	$T_1 - 2.0$ $T_2 + 1.0$ $T_3 + 3.0$
39.	$T_1 + 0.5$ $T_2 + 3.0$ $T_3 + 3.5$	1 hour	$T_1 + 0.25$ $T_2 + 0.25$ $T_3 - 0.25$
40.	$T_1 + 1.25$ $T_2 + 1.75$ $T_3 + 0.25$	1 hour	$T_1 + 0.25$ T_2 — T_3 —
41.	$T_1 + 2.0$ $T_2 + 3.0$ $T_3 + 1.75$	1 hour	$T_1 + 0.5$ $T_2 + 0.75$ $T_3 + 0.25$
42.	$T_1 + 2.5$ $T_2 + 2.5$ $T_3 - 0.5$	30 min.	$T_1 + 0.5$ T_2 — $T_3 - 0.25$
20 minutes			
		Before adrenaline	After adrenaline
43.	$T_1 + 3.0$ $T_2 + 1.5$ $T_3 - 1.0$	$T_1 + 1.0$ $T_2 + 0.5$ $T_3 - 0.5$	$T_1 + 3.5$ $T_2 + 2.0$ $T_3 - 1.0$
44.	$T_1 + 1.5$ $T_2 + 2.0$ $T_3 + 1.0$	$T_1 + 0.75$ T_2 — $T_3 - 0.25$	$T_1 + 2.0$ $T_2 + 2.0$ $T_3 - 0.5$

is very variable, and we would seriously question the previously accepted statement that the inversion usually begins

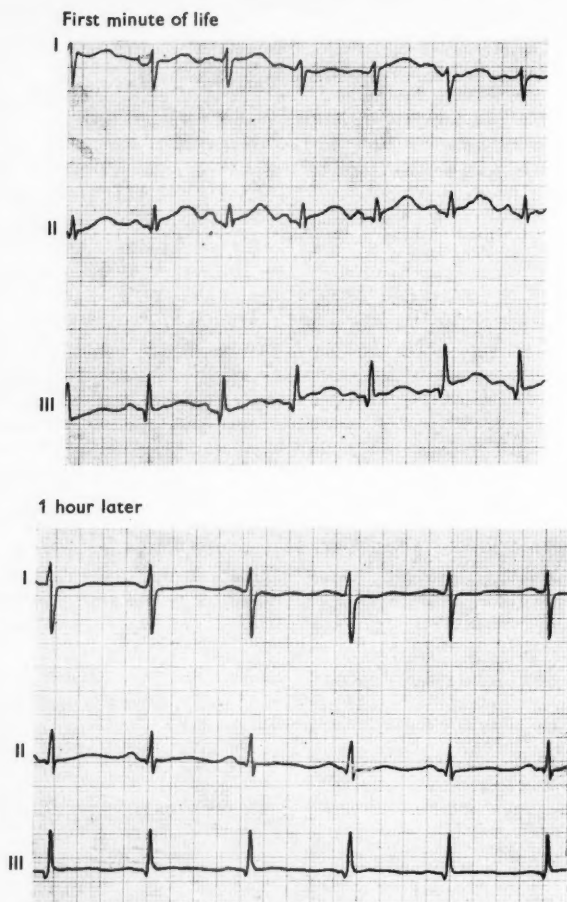


Fig. 1. Changes in *T* waves after birth.

The top tracing taken in the first minute of life shows good amplitude *T* waves in all three standard leads. The tracing taken 1 hour later, and shown in the bottom part of the figure, shows the *T* waves to be flattened.

at 24-48 hours and is completed in 4-7 days (1).

As shown in the table, our tracings reveal the presence of a negative Tv_1 as early as 30 minutes after birth, many showing good evidence of inversion before 24 hours of age. We are unable to distinguish on the basis of *T* wave inversions,

"difficult" from "normal" deliveries, and were unable to correlate either the speed or magnitude of the inversion process with the clinical status of the infant.

As regards the *T* waves in the extremity leads, it can be seen from Table 2 that there are marked changes in *T* wave amplitude occurring shortly after birth, with

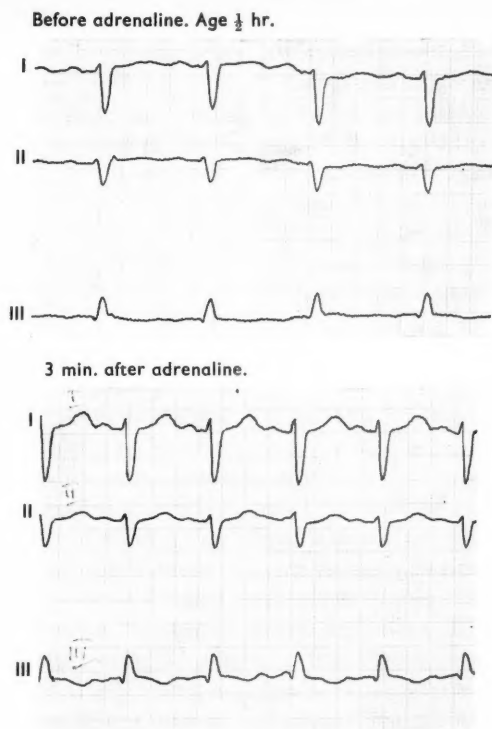


Fig. 2. *Effect of adrenaline on T waves.*

The top tracing is that of a 20 minute old infant who had good *T* waves at birth. Tracing at 20 minutes shows flattened *T* waves. In the bottom tracing, taken 3 minutes after the I.M. administration of 100 micrograms adrenaline, the *T* waves are now easily evident.

the tendency towards decreasing amplitude and flattening of the *T* waves. (Case 38 exhibited marked changes of inversion of the *T* waves rather than flattening but was unfortunately not followed beyond the 1 hour period.) An example of these *T* wave changes is shown in Fig. 1.

In an effort to determine the time relationships of these changes, serial studies were made on infants. These show changes of marked flattening of *T* waves as early as 4 minutes after birth. Three children, followed for two hours, exhibited the flattening at the same time that the body

temperature was falling. In two of them the temperature had dropped by more than one degree centigrade within 1 hour after birth. However, the attempt to influence the ECG pattern in the reverse direction by heating the infants was unsuccessful, as was a similar attempt to prevent the changes by keeping the body temperature at a higher level than normal by means of surrounding water bottles and an incubator.

As in the first group of infants, we were unable to distinguish the clinical state of the infant from the extent or timing of the

T wave changes, as these occurred in all infants regardless of the clinical state.

In two infants given 100 micrograms of adrenaline I.M., a striking increase in the amplitude of *T* waves was noted. Both of these infants had exhibited good amplitude *T* waves at birth only to have them diminish within 20 minutes after birth. The adrenaline effect occurred within 2-3 minutes after injection and persisted for approximately 1 hour (see Fig. 2).

Discussion

The etiology and significance of the neo-natal *T* wave alterations has been much discussed in recent years. It may, therefore, be helpful to briefly review the information available, and the ideas postulated for the changes. Prior to this report, however, the question of change has been confined to the unipolar leads, the assumption being that the extremity lead *T* pattern was of low amplitude from birth on.

The discussion has until now naturally centered about the concept of closure of the ductus arteriosus. Thus Brown (7) believes the phenomenon to be in some way related to the closure of the ductus. Ziegler (1) has pointed out that the effect on the ECG appears comparable to that occurring in the hypoxia tolerance test prior to ligation of a patent ductus in older children (8). Rowe & James (9), working with mongols and Adams & Lind (27) with normal newborns have shown on the basis of cardiac catheterization, that the pulmonary arterial pressure falls in the first few days after birth, this fall

occurring during the time of change-over of Tv_1 , and Rowe has recently expressed the view that there is a significant fall in pulmonary arterial pressure within the first hour after birth (24). Similarly, Dawes and his co-workers have shown the pulmonary arterial pressure in the newborn lamb to fall within a few minutes after the lungs have been ventilated (10).

Among other relationships mentioned, the idea of early transient anoxaemia due to shunting via a foramen ovale or pulmonary atelectasis has evolved as a cause for the changes. However, efforts to influence the changes by administration of oxygen have been notably unsuccessful (11). Sodi-Pallares (2), has also pointed out a difference in the negative Tv_1 of infants which he calls a physiologic infantile *T* wave as opposed to the pathologic negative *T* wave of myocardial ischaemia. In his view, the "normal" physiologic negative Tv_1 is both asymmetrical and its ascending limb ends in a slight positivity, whereas the pathologic one lacks these features.

The proposition that the *T* changes are an expression of neo-natal right ventricular hypertrophy deserves mention. The fact that the changes occur with such rapidity speaks for a physiologic rather than an anatomic causation. In addition, the premise on which it is based, i.e. that in young children the *T* waves in V_1 are always positive in the presence of R.V.H. (12) is not universally applicable as negative *T* waves can be found in cases of pure pulmonic stenosis showing marked evidence of R.V.H. both radiographically and on the ECG.—Statistical analysis of the behaviour of Tv_1 in infancy and early childhood has shown that the incidence of

a positive T in V_1 as a sign of right ventricular hypertrophy varies inversely with the other two accepted ECG signs of R.V.H. (i.e. increased R/RS/ratio, and prolonged ventricular activation time) (25, 26).

Dupuis et al. (11) investigated the effect of adrenaline, acetylcholine, 10 % O_2 , and 100 % O_2 on the ECG. The last three produced no significant changes. To six infants between 5 and 10 days of age they gave 50 micrograms of adrenaline, either I.M. or I.V. Changes in Tv_1 were observed in all. They were able to convert the negative Tv_1 to positive in one case and the pattern became diphasic with a predominantly positive component in the other 5. Of additional interest in this experiment is the fact that during the period of circulatory adjustment the newborn infant's cardiovascular system responds to adrenaline with an increase in right ventricular and pulmonary arterial pressure (13), thus indicating a possible relationship between adrenaline, pulmonary arterial pressure, and the ECG changes in Tv_1 .

With respect to the standard limb leads, the situation differs somewhat. Our findings would indicate that the until now noted flattened T waves are not flat immediately at birth but become so shortly thereafter. Michaelsson (3) has recently reviewed the ECGs of newborn infants, and makes the observation that the T waves are flat. However, the youngest infant in his series was 30 minutes of age when the first tracing was taken. It is interesting that in the series of infants reported by Zitka & Papez (14) concerning the influence of the first breath on the ECG, tracings taken before and immediately after the first breath, show the pre-

sence of good T waves at birth and immediately afterwards.

Various explanations have been offered for the apparent flat T waves in the neonatal extremity lead ECG. Thus in 1935, Hori, Imai & Sato (15) noted "the absence of demonstrable T waves in standard limb leads in a majority of infants between 1 and 24 days of age. They suggested this to be indicative of myocardial disease, presumably on an anoxic basis. The idea of anoxia as the basis for the change has recently found support in the work of Ringel (16). He reports no effect seen in asphyxiated children in tracings taken after the period of asphyxia was over and the infant had been successfully resuscitated. However, in older infants, induced hypoxia (tent with 10 % O_2 and 90 % N_2), caused flattening of the T waves. On a rebreathing test (CO_2 intoxication) he noted that 50 % of previously normal infants now had flattened T waves, as in newborn infants. He considered these changes to be transitory and relatively instantaneously removable on removing the stimulus, and proposes anoxia as the pathogenic agent of the flattened neo-natal T waves.

Our findings do not support anoxia as the cause of the neo-natal flattening to the extent that we were unable to distinguish, on the basis of the T wave pattern, asphyxiated from apparently normal infants in tracings taken during the actual time of asphyxia.

Temperature variations have been investigated with respect to ECG changes, and have been shown to produce T wave changes in rats (17). However, Joppish & Stoermer (18), have shown that in infants the physiologic lowering of the tem-

perature, while it will prolong the QT interval, has no effect on the *T* waves themselves. These findings are supported by our own inability to alter the *T* waves either by lowering or raising the environmental temperature.

The position of electrolyte changes as being a responsible agent remains unclear. McCance & Widdowson (19-22) have written extensively concerning the water and electrolyte changes of the newborn. However, to the present authors' no satisfactory correlation between these changes and the ECG has been demonstrated.

In the present study, we were able to produce *T* waves in the ECGs of the two 20 minute old infants whose immediate post-natal *T* waves had become flattened, with the passage of time, by the administration of adrenaline. Added to the results of Dupuis et al. (11), who were able to influence *Tv*₁ by the same means, this would indicate an etiologic role either to adrenaline itself or to a physiologic process which can be simulated by adrenaline administration. The possible role of the change in pulmonary arterial pressure has already been mentioned. It is interesting to note also that recent work by Ashworth & Neligan (23) has demonstrated a fall in peripheral blood pressure during the first few hours after delivery in normal babies, sometimes to little more than $\frac{1}{2}$ the initial value, with the highest reading

usually recorded in the first 15 minutes after delivery. Since the peripheral blood pressure may also be influenced by adrenaline, this gives further impetus to the idea of adrenaline or an adrenaline reproducible effect as being the possible etiologic agent in the *T* wave alterations.

In view of these findings, it would be interesting to compare levels of catecholamines in the first and subsequent urine specimens of the newborn infant, as well as in the mother. Work along these lines is currently in progress at this center.

Summary and Conclusions

A report of the *T* wave alterations in the ECG of the newborn infant is presented. We confirm the previously described inversion of the *T* wave in lead *V*₁, with the proviso that the inversion often occurs much earlier than has previously been supposed.

Our findings show the *T* waves in the extremity leads immediately after birth to be of good amplitude, but to undergo flattening within a matter of minutes after birth occurs. The administration of adrenaline to two infants resulted in a temporary return of *T* waves of good amplitude.

Possible etiologic factors in the changes are discussed and new avenues of research are indicated.

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Marbling and Perinatal Anoxia

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Introduction

A syndrome of choreo-athetosis and mental deficiency with marbling ("status marmoratus," "état marbré"—descriptive terms for a network of scarring) of the basal ganglia was first described by C. Vogt (1912) and later C. & O. Vogt (1920).

Since then many cases have appeared in the world literature. Meyer & Cook (1935) found that 23 cases had been verified pathologically. Carpenter (1950) was able to review 42 cases. British literature of recent years has contained detailed descriptions of similar cases (9, 10, 11).

The purpose of this paper is to present clinical and pathological findings in three mentally defective children, who had typical état marbré. In each case there was a clear history of birth anoxia due to circulatory obstruction of the umbilical cord and the severe asphyxia which resulted was considered to be the cause of the marbling. One child had a prolapse of the cord, another had a firm true knot and one had the cord wound tightly round the neck.

Case 1

This was an imbecile boy with athetosis and spastic diplegia, whose backwardness was suspected from 9 months of age and who died at 3 years and 7 months of broncho-pneu-

monia and subarachnoid haemorrhage. He was the result of a healthy mother's sixth pregnancy during which she felt well until the 36th week when she had a slight antepartum haemorrhage which was regarded as insignificant. The head remained high and could not be engaged at 38-40 weeks. Cephalometry revealed a large foetal head with a bi-parietal diameter of 9.9 cm (normal range 8.0-10.8 cm). Rhesus antibodies were not demonstrated. The mother's blood group was A. Labour began spontaneously and lasted 27 hours and 30 minutes. After 25 hours of the first stage the head remained high with the cervix 3 to 4 fingers dilated. The membranes ruptured and vaginal examination revealed a prolapsed pulsating cord. Two hours later foetal distress became evident and the cord ceased to pulsate but the cervix was only 4 to 5 fingers dilated. The cord was pushed up beside the head and began to pulsate again. Anaesthesia was induced and forceps applied after stretching the cervix; the cord remained above the head. Delivery was completed without difficulty in 15 minutes, but the infant was born in a state of "white asphyxia." After clearing the airway, the larynx was intubated and lobeline given intravenously; 10 minutes later gasping respirations began. The infant weighed 4910 g, and was restless for the first 48 hours. The biparietal diameter was 10.5 cm, the suboccipito-frontal diameter 12.4 cm and the head circumference 30.8 cm.

The mother's fourth pregnancy ended at 3 months, her fifth pregnancy resulted in a full-term hydrocephalic stillborn infant. Four



Fig. 1. Case 1. A coronal section through the thalamus and basal ganglia revealed that the effect of marbling was created by dark reticulated areas in the thalamus (T) and lentiform nucleus (L). Holzer $\times 2$.

surviving children were physically and mentally normal.

Attention, in this paper, is confined to the necropsy findings in the nervous system. The brain appeared large and oedematous. A large subarachnoid haematoma extended over both parieto-occipital regions and the right frontal area. Over the vertex, bleeding had been more recent. In the left parietal region there was a large area of necrotic brain tissue with "chocolate-like" material, which flowed out easily once the brain was disturbed. There were a few ml of bloody fluid in the lumbar space; the cord itself appeared normal. The meninges were slightly thickened and congested with dilatation of the vessels over the surface of the brain, especially along the longitudinal sinus. When dissected, the right hemisphere looked smaller than the left. All the cortical veins were intensely congested and possibly thrombosed. The meningeal haemorrhages, especially behind the central fissure, extended into the brain. A smaller haemorrhage had destroyed part of the right frontal

pole. The lateral ventricles were dilated but the aqueduct was patent. The corpus callosum was thinned in its middle-third. *État marbré* was present in the thalami and the lenticular nuclei, these areas being much paler than normal. The fixed brain, with the cerebellum and brain stem, weighed 1 020 g (normal for age 1 064 to 1 141 g).

Histological features

After fixation in 10 per cent formal-saline, coronal blocks of the frontal, temporal and occipital lobes, the basal ganglia, the cerebellum, a sagittal block of the parietal lobe and representative levels of the brain stem and spinal cord were embedded in celloidin. Sections were stained by the Nissl, van Gieson, Mallory's P.T.A.H., Heidenhain and Holzer techniques. Frozen material was used as required and stained by the Holzer, Nissl, Heidenhain, Kultschitsky-Pal, Bielschowsky, von Kossa, Gomori and Sudan III methods. Frozen material was also examined under a polarizing microscope. Similar techniques were applied to subsequent cases.

Apart from the subarachnoid bleeding, the most striking feature was bilateral and symmetrical marbling in the thalami and basal ganglia (Fig. 1), which affected the dorsal two-thirds of the medial and lateral thalamic nuclei, the dorsal halves of the globi pallidi and the dorsal thirds of the putamina. The marbled appearance was due to the reticular affect created by whorls of dense glial fibres (Fig. 2). Nerve cells were lacking where gliosis was complete but amongst some interstices on the glial strands a few islands of nerve cells had survived (Fig. 3). Bielschowsky's technique showed that the gliosed areas consisted of a tangled mass of fine fibres originating from fibrous and cytoplasmic astrocytes and which contrasted with the more orderly arranged nerve fibres of a control adult thalamus. The internal and external medullary laminae of the thalamus were not demonstrated.

There was a reduction of nerve cells in the frontal cortex particularly in Layer 3. A patchy loss of nerve cells was present in



Fig. 2. Case 1. Reticulation of glial scars (marbling) in the dorso-medial thalamic nucleus. Holzer $\times 12$.

Layers 3 and 4 of the temporal lobe and the uncus.

Gliosis was slightly increased subependymally around the ventricular cavities. Gliosis affected the reticulated area of the substantia nigra, where it was quite dense, and also the mesial filets and cortico-spinal tracts. It was present in the nucleus intercalatus, nuclei pontis, restiform bodies, reticular formations and inferior olivary nuclei. Small amounts of gliosis were present in the white matter of the cerebellar folia.

Case 2

This was an idiot boy with spastic quadriplegia who died suddenly at the age of 11 months. He was the result of a healthy mother's second pregnancy which proceeded normally to term. When labour began, all seemed well till the beginning of the second stage two hours later, at which time the mother became restless and foetal distress was evident. A low forceps delivery was per-



Fig. 3. Case 1. A neighbouring section from the same block as Fig. 2., each small dark dot was a nerve cell. Normally, the whole section should be so dotted but nerve cells were absent from the scarred areas and only small foci of intact cells remained. Nissl $\times 12$.

formed without difficulty under general anaesthesia. The infant was in white asphyxia due to a firm knot in the umbilical cord which had ceased to pulsate. After resuscitation the child was extremely stiff and developed opisthotonus. A neo-natal streptococcal skin infection developed, from which an uneventful recovery was made.

The fixed whole brain with cerebellum and brain stem, covered by translucent meninges, weighed 750 g (normal for age 809 to 852 g). The right hemisphere appeared slightly smaller than the left. All the cranial nerves were present. The main vessels at the base of the brain were normal but there was moderate congestion of the surface vessels. There was slight ventricular dilatation. Both thalami, especially the right, looked very white and the normal pattern was distorted and the



Fig. 4. Case 2. A coronal section through the thalamus and basal ganglia revealed dense glial scarring (marbling) of the thalamus (T), lenticular (L) and caudate (C) nuclei. Mallory $\times 2$.

grey matter replaced by whorls of glial tissue; posteriorly towards the pulvinar the pallor was more symmetrical.

Histological features

The most striking feature was marbling of the thalamus and basal ganglia (Fig. 4), the right side being more extensively involved than the left. The dorso-medial and dorso-lateral thalamic nuclei, the dorsal two thirds of the putamen, the globus pallidus, the head of the caudate nucleus and the zona rubra were densely gliosed in a manner very similar to that in Case 1. There was a widespread loss of nerve cells which were replaced by fibrous astrocytes, but, in the midst of dense gliosis, islands of normal cells were seen. As in Case 1, the internal and external medullary laminae of the thalamus were not demonstrated. Many doubly refractile bodies were present in the putamen and globus pallidus and in the same areas there were large numbers of sudanophilic globules of varying size. Rounded and oval deposits of "pseudocalcium,"

which stained uniformly blue with cresyl violet and dark brown with haematoxylin, were scattered lightly throughout the putamen and thalamus. Their size varied, some were similar in size to the nuclei of astrocytes, others were two or three times larger. They did not have any constant relationship to blood vessels. Iron deposits were not demonstrated.

A fine fibrous gliosis involved the internal capsule, corpus callosum, corona radiata, dentate gyrus and Ammon's horn. It was also seen amongst the fibres of the inferior olives and reticulated area of the substantia nigra. "Plaques fibromyéliniques" were present in the marginal gyrus, being most pronounced in Layers 3 and 4 where they consisted of whorls of densely packed glial fibres. Many strands of these fibres extended either into adjacent white matter or to the cortical surface which they had puckered. Astrocytes were increased amongst the glial tissue and nerve cells had completely disappeared but, in the interstices of the scars, nests of surviving nerve cells were seen parallel to the course of blood vessels. The affected gyrus was much reduced in size and irregular, as a result of these changes.

Nerve cells in Layers 3 and 4 of other parts of the cortex were diminished in numbers, especially in gyri on the medial aspect of the hemispheres, insula, Ammon's horn and geniculate bodies.

Case 3

This was an epileptic idiot boy, with choreiform movements and spastic diplegia, whose backwardness was first suspected in his second year and who died of bronchopneumonia at 3 years and 11 months. He was the firstborn infant of an unmarried mother whose mentality was thought to be poor but in whom adequate testing had not been done. Pregnancy proceeded normally to term and the infant was delivered spontaneously after a labour lasting 13 hours (second stage 1 hour and 20 minutes). The infant, weighing 3100 g, suffered from white asphyxia due to the cord being wound

tightly round the neck. After removal of the cord and oxygen therapy, improvement was rapid.

Weighing 844 g, with cerebellum and mid-brain, the fixed brain was lighter than the average for the age—1 141 g. The external general formation was normal but ulegyria affected the anterior parts of the inferior and middle temporal gyri and the inferior frontal gyri. Thickened opaque meninges covered all aspects of the frontal and basal areas and in the fresh state appeared turbid and oedematous. Blood vessels and cranial nerves were normal. The ventricles were enlarged but the foramina of Monro and the aqueduct of Sylvius were patent to a normal extent. To the naked eye, the thalami and basal ganglia seemed normal.

Histological features

Marbling was less extensive than in the previous two cases but was present in the extreme capsule, the external capsule and claustrum. There was a distinct pallor of the myelinised tracts in the extreme and external capsules, a few remaining fibres showed irregularity of calibre and beading. Nerve cells were few in the claustrum. These areas were infiltrated by many astrocytes and fine glial fibres intersecting in all directions except those in the extreme capsule where they were condensed into a dense sheet running parallel to the course normally taken by myelinated fibres. There was an anomaly in the findings in the thalami because there was a reduced number of nerve cells and replacement by astrocytes, yet, by the methods used, glial fibres were not demonstrated. Most of the surviving nerve cells were normal but a few were pyknotic. Pseudocalcium deposits were scattered liberally throughout the lateral thalamic nuclei where nerve cell loss had been greatest but doubly refractile bodies, and an excess of neutral fat, were not found.

Nerve cells were reduced in Layers 5 and 6 of the inferior frontal gyri and gyri in the area of the central sulcus, where multiple semilunar glial scars, 2 to 3 mm long, were

present and which, in contracting, had puckered the surface of the cortex. A fine fibrillary gliosis affected the dentate gyri.

Gliosis was increased around the ventricles and many ependymal granulations were noted. There was a fine diffuse gliosis in the corona radiata. The reticulated area of the substantia nigra and pontine nuclei were also gliosed.

Discussion

Coiling of the foetal cord around the neck is a common event, for instance, Shui & Eastman (14) quoted an incidence of 23.3 per cent amongst 1 000 consecutive deliveries. However, opinions differ as to the frequency and significance of complications resulting therefrom, for instance, Shui & Eastman (14) questioned the tendency to attribute unexplained foetal deaths to this complication whereas Whitehouse (16) during an investigation of 100 cases of foetal distress attributed 24 of them to cord round the neck. Cord prolapse was reported by Gibberd (5) to be 0.33 per cent amongst an average group of patients, but the infant mortality was 80 per cent. Mengert & Longwell (6) gave an incidence of cord prolapse of 0.37 per cent in head, 4.54 per cent in breech and 14.57 per cent in transverse presentations. True knots of the cord are rare. Potter (12) reported the mortality rate from cord complications to be 2.9 (1931–1941), 1.6 (1941–1946), 1.6 (1946–1949) per 1 000 births.

Cord complications were known to have occurred in 7 other patients who had been admitted to the Fountain Hospital during the ten year period from 1948 to 1957. Their inclusion makes the incidence of mentally defective children with umbilical cord complications 1.1 per cent amongst

1 058 admissions. It is appreciated that the history of a cord complication at birth may not necessarily indicate the cause of a child's illness, for instance in one of the mentioned 7 cases it was probably of no significance since birth asphyxia was absent. Moreover, it was difficult to determine what role the cord complication played when other complications were present.

The cause of marbling, on the other hand, is not always obvious. In addition to the reported cases, marbling was found in the thalamus and basal ganglia of five other children. This made an incidence of 9 cases out of 282 necropsies or 3.2 per cent over a 10-year period, and disregards other cases in which there was marbling of the cortex but not of the basal ganglia. Two of these children were premature and suffered from birth anoxia due to other causes than obstruction to the circulation in the foetal cord; one child had kernicterus due to rhesus incompatibility, but in the other two children there was no known incident in the perinatal period to which their lesions could be attributed.

The view is taken that birth asphyxia, resulting from circulatory obstruction of the umbilical cord, caused the lesions in these four children. Some confirmation for this was sought in the observations of Meyer (7) who found a regional vulnerability of the brain due to the effects of anoxia in which nerve cells were lost in the cortex, Ammon's horn, globus pallidus, cerebellum and zona rubra. A different view has been expressed by Norman (9, 10) and Norman, Ulrich & McNemeny (11). They offered a more mechanical explanation for their cases and felt that, as

the venous drainage of the thalami, lentiform and caudate nuclei was into the vein of Galen, disturbances in this "watershed," created at birth by distortion of the straight sinus during abnormal delivery of the head, resulted in marbling.

Marbling was thought by Alexander (1) to be due to aberrant fibre tracts but no aberrant tracts were seen in the present cases, by contrast, normal tracts such as the internal and external medullary laminae of the thalami were absent in two cases. Hypermyelination has often been regarded as responsible for the striking picture and Denny Brown (4) concluded that, since deposition of myelin is a function of glia, the primary disorder may be a specific variety of gliosis. While it was true that the marbled areas in the present cases had some affinity for myelin stains such as that of Heidenhain, it was found that by adequate progressive differentiation, the marbled areas lost the stain before the usual myelin tracts. After careful scrutiny with further staining techniques, it was concluded that the principle component of the marbled areas was gliosis and not hypermyelination.

Bullough (2) described normal development at one year in a boy who had a pulseless prolapsed cord and subsequent asphyxia for 30 minutes, for which he received endotracheal and intragastric oxygen. Reiss (13) reported a successful outcome in a boy who had a pulseless foetal cord coiled tightly around the neck five times and who at one year was developing normally (Smellie (15)). Thus the outlook for infants who suffer from birth incidents similar to those of the presented three boys may not always be gloomy.

Summary

The clinical histories and physical findings are presented of 3 mentally deficient boys, in each of whom there was a story of perinatal asphyxia due to circulatory obstruction of the umbilical cord. One child had a pulseless prolapsed cord, one had a pulseless cord due to a firm knot, and one had a pulseless cord due to the cord being tightly round the neck.

The pathological findings in the nervous system are described. All the 3 children had small brains. In 2, striking marbling of the thalami, the putamina and globi pallidi was seen. These 2 cases also had loss of nerve cells in the cortex insula and Ammon's horn. Gliosis was also present in the reticulated area of the substantia

nigra, the inferior olives and periventricular gliosis was increased. It was concluded from staining characteristics that damage in these areas had resulted in dense gliosis. In one child, damage to the thalamus and basal ganglia was present but to a less striking extent and multiple foci of gliosis were seen in the grey matter of the frontal and parietal cortex.

This work is a shortened form of an essay which was written for, and awarded a prize in, the South West Metropolitan Regional Hospital Board's 1958 Competition for Research Reports.

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Respiratory Studies in Newborn Infants

I. Apparatus and Methods for Studies of Pulmonary Ventilation and the Mechanics of Breathing. Principles of Analysis in Mechanics of Breathing.¹

by PETTER KARLBERG, RUTH B. CHERRY,² FLORENCIO ESCARDÓ³ and GÜNTER KOCH⁴

Respiration is from a clinical viewpoint one of the most important functions in a newborn infant. Within the first minutes of life the newborn has to establish adequate pulmonary function, and if he does not his continued existence is jeopardized. In many cases signs and symptoms of respiratory distress appear and this accounts for most of our neonatal deaths. Many other neonatal diseases which are not primarily pulmonary also express themselves first as respiratory disturbances. The problem of evaluating pulmonary function in the newborn has been studied in this laboratory, some of the work being a continuation of respiratory studies begun by two of the authors in Dr. Clement A. Smith's laboratory in the Boston Lying-in Hospital.

This report describes the chief apparatus and methods used in these studies.

¹ One of a series of studies supported by research grants from the Swedish Medical Research Council and from the Association for the Aid of Crippled Children, New York City.

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⁵ Throughout this paper the symbols employed to denote respiratory variables are those suggested for purposes of standardization by a group of clinical and research respiratory physiologists headed by J. R. Pappenheimer (12).

Even if all are not used in each study, we have considered it practical to present them together in the first paper of a series planned for this journal.

The laboratory equipment has been designed for the study of:

1. Pulmonary ventilation, including minute volume (\dot{V}),⁵ tidal volume (V_T) and respiratory rate (f) during short and long periods of time.

2. Gas exchange, oxygen consumption (\dot{V}_{O_2}) and CO_2 production (\dot{V}_{CO_2}).

3. Respiratory pattern.

4. Mechanics of breathing.

These studies may be performed while the infant is breathing room air or other gas mixtures. All these determinations require a recording of the volume changes during respiratory cycles, correct in phase (without time lag) and amplitude. A derivation of these volume changes gives a flow rate record; an integration, a minute volume record. A simultaneous recording of the intraesophageal pressure changes allows the study of the mechanical forces involved during pulmonary ventilation. Some kind of a mask or hood is necessary for gas exchange determinations and for giving the infant different gas mixtures to breathe.

Volume recording

An accurate recording of respiratory volume changes has been based on the pressure changes resulting from the addition or subtraction of volumes of air displaced by

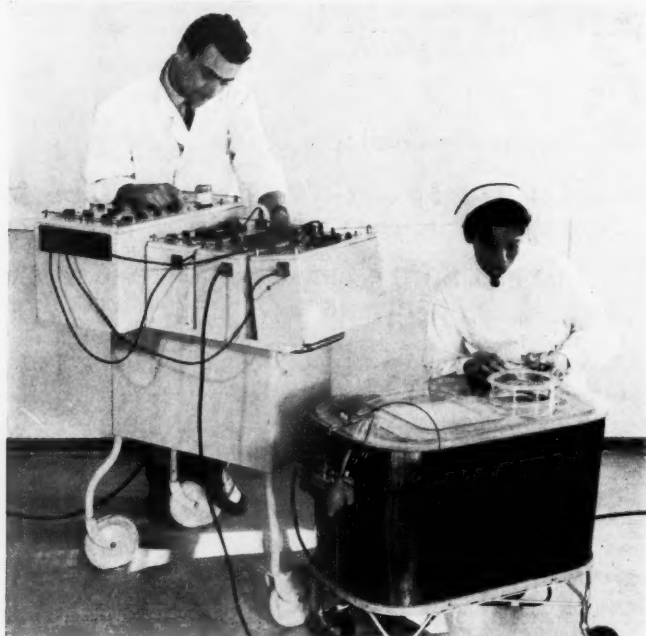


Fig. 1. Body plethysmograph system.

the infant's respiration to or from a closed system containing a relatively large volume. For studies of long duration during standard resting conditions, a body plethysmograph similar to those of Cross (4) and Cook *et al.* (1) has been used. To keep the infant's body temperature constant even during considerable periods of time, the plethysmograph was built from an old type incubator which consists of an open copper bathtub-like box with double walls containing electrically heated water (Fig. 1). The infant lies on his back on a hammock-like bed with his face emerging through a pneumatic ring in a plastic frame. The ring is sealed to the face and the frame with an aquaresin-glycerine mixture.¹

The plastic lid of the plethysmograph is

¹ Aquaresin, obtained from the Glyco Products Co., Empire State Building, New York 1, is mixed with equal parts of glycerine. This provides an effective seal without damaging the rubber cuff.

made in several parts in order to facilitate the handling of the infant. The plastic parts are sealed together with an aquaresin-glycerine mixture, and a heavy weight placed on top. The mattress and pillow are inflatable and their thickness can be adjusted from outside in order to position the face relative to the pneumatic ring and frame. If necessary, the infant can be taken out rapidly.

The respiratory movements of the infant's chest and abdomen reflect the pulmonary volume changes and cause small pressure changes within the constant volume of the airtight plethysmograph (less than ± 0.5 cm of H_2O during quiet breathing). Such changes are transmitted to an electromanometer by a stiff tube passing through the lid.

The O_2 consumption and CO_2 production are determined using a technique previously reported (1, 5). A plastic face mask with a volume of approximately 60 ml is sealed to the pneumatic ring with an aquaresin-

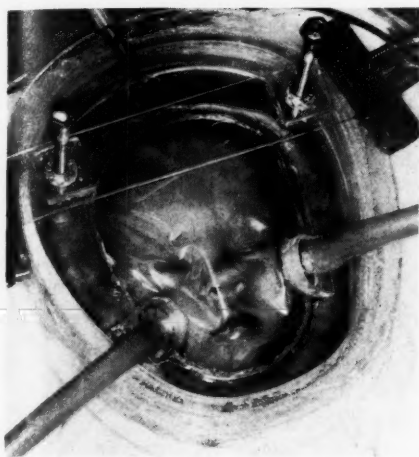


Fig. 2. Sealing of infant's face in body plethysmograph and face mask for gas exchange studies.

glycerine mixture (Fig. 2). By means of a pump compressed air or some other nitrogen-oxygen mixture is drawn, together with the expired air, across the infant's face and collected in plastic bags. At a rate of 5 to 6 liters per minute, analysis of the air in the mask has not shown more than 0.3 volume

per cent of CO_2 during studies of quietly breathing newborns. The gas analysis and calculations are performed in the usual manner for an open basal metabolism system.

During short periods of volume recording when resting conditions are not required or there is too short a time for adjusting the infant in the body plethysmograph, a "reverse plethysmograph" system was used.

A plastic mask with a rubber ring is held against the infant's face covering the mouth and nose, and sealed with a thin layer of aquaresin-glycerine (Fig. 3). The mask is connected to a 65 liter glass bottle via a 35 mm inside diameter stiff-walled rubber tube (Fig. 4). The pressure changes caused by the infant's breathing into the closed system are detected by an electromanometer (the same one used with the body plethysmograph). A certain amount of rebreathing from the mask and tube slowly increases the CO_2 content inside the system, but it can be neglected during recording times of one half to one minute. A small increase in temperature of the air in the mask and the connecting tube has no measurable influence on the volume recording. However, the air inside the glass bottle must not be exposed to sudden temperature changes.

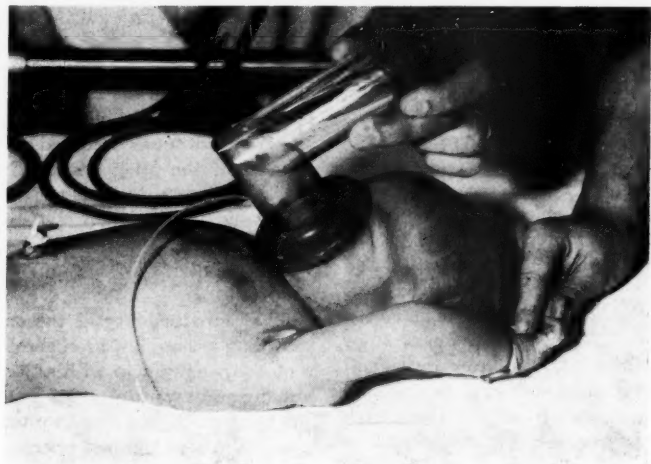


Fig. 3. Attachment to infant (face mask with intraesophageal polyethylene catheter).

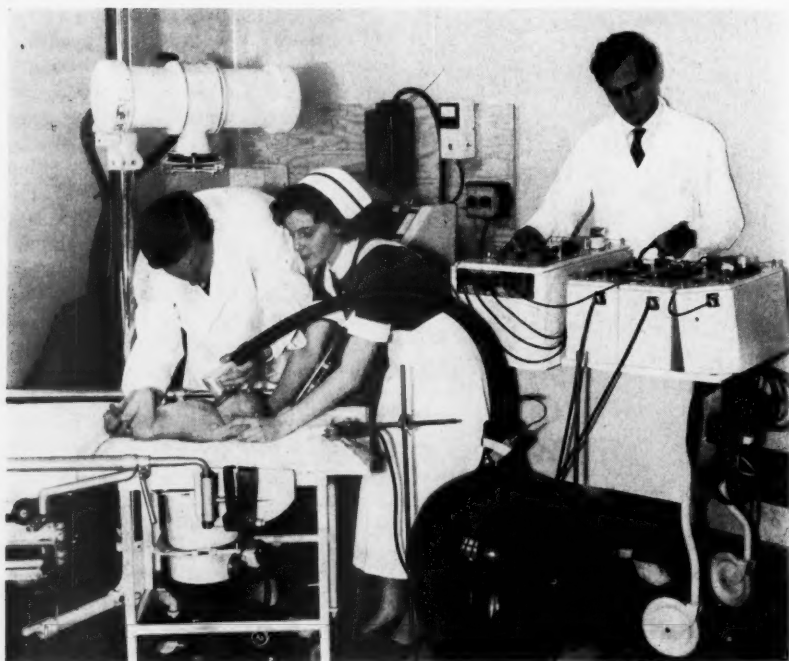


Fig. 4. Reverse plethysmograph system.

Electrical recording system

The electromanometer, which picks up pressure changes in either the body plethysmograph or the 65 liter bottle used in the second method described, is of the strain gauge type with a carrier frequency amplifier (Elema).

The amplified signals are recorded on one channel of a four channel direct writing recorder (Elema's Mingograph) and give a volume change curve. The signals are also transferred to a specially constructed electronic device¹ (Fig. 5) for derivation of a flow rate curve and for integration of 30 or 60 second intervals. The latter gives half or one minute volumes. This device also records the number of breaths where each breath exceeds an adjustable minimum tidal volume, with each of these breaths an equal

step in a step-ladder curve. The total deflection of this curve during a certain time interval (one half or one minute) is directly related to the respiratory frequency. The amplification of each of these three signals (\dot{V}/t , \dot{V} , f) can be adjusted independently and each output is recorded on a different channel of the Mingograph. The recording paper runs at adjustable speeds: 2.5, 5, 10, 25, 50 and 100 mm/sec.

Reproducibility and calibration

The reproducibility of the entire volume recording system has been checked by using a glass syringe pump with adjustable stroke volume and rate (up to 200 per minute). In the body plethysmograph system the pump is connected to the face opening and in the "reverse plethysmograph"-system to the face mask.

¹ Designed by R. Elmqvist, M.D., Elema.

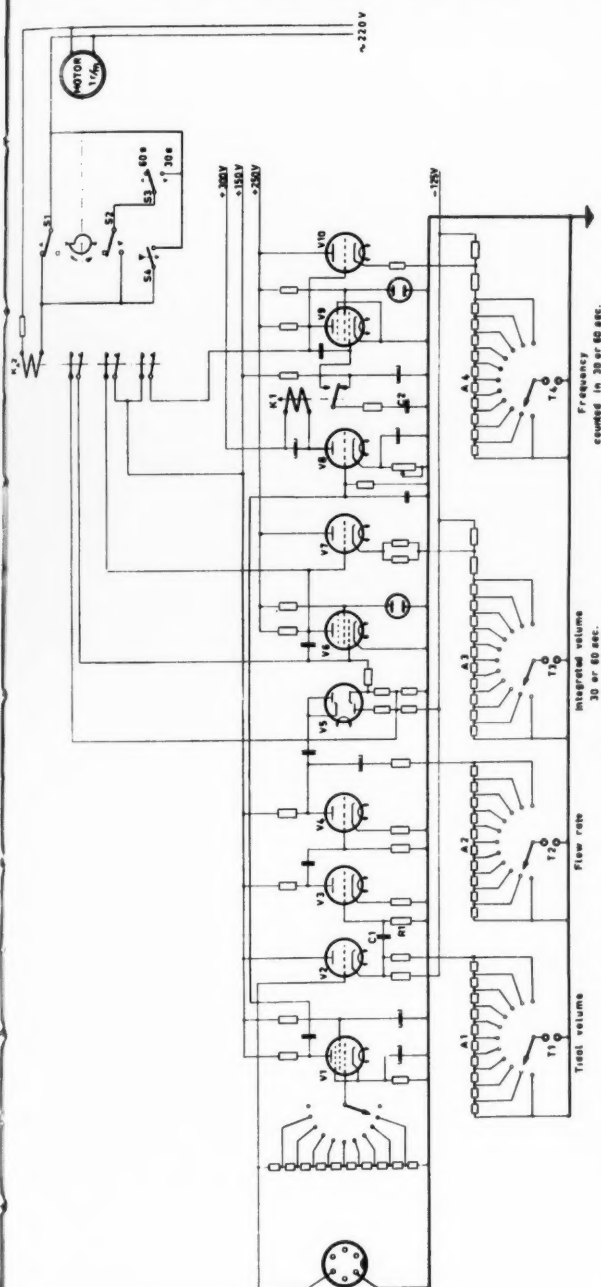


Fig. 5. A schematic diagram of the electronic device specially constructed for the recordings. From the receptacle at the left the signal reaches the grid of a cathode follower V 2. The terminals T 1 are connected to the dc amplifier of one of the channels of the Mingograph. The amplitude of the signal can be adjusted by means of attenuator A 1. Part of the signal is taken off from the cathode of V 2 and is differentiated in the network C 1, R 1. The time constant of this network is 0.008 s, which is sufficiently low for differentiating even the highest frequencies of respiration observed. In order to compensate for the attenuation in the differentiating network the differentiated signal is again amplified in an amplifier consisting of the tubes V 3 and V 4. The coupling networks of this amplifier have very high time constants. The output has an attenuator A 2 and from the terminals T 2 a voltage proportional to the flow rate is fed to the recorder.

In order to get the integrating volume, part of the flow rate voltage after being rectified in V 5 is fed to the grid of the Miller integrator V 6. The anode of the integrating tube is connected to another cathode follower tube with attenuator A 3 and output terminals T 3. The average respiratory frequency during the period of integration is obtained from a second integrator V 9 with cathode follower V 10, attenuator A 4 and output terminals T 4. The input voltage is amplified in V 1 and coupled to the grid of V 8 which is biased to cut off. The positive half-wave of every breath makes V 8 conducting and switches the condenser C 2 from its charging source (150 volts) to the grid of V 9 by means of the relay K 1. Thus every breath transmits an equal charge to the integrator V 9 and the output voltage is proportional to the number of breaths after the last resetting of the integrators. The resetting of the two integrators is governed by a synchronous motor (1 rpm) actuating two switches S 1 and S 2 placed 180° apart. Every switching closes the contacts of the relay K 2 for a short time and the integrators are reset every 30 seconds. If the switch S 3 is opened, resetting occurs only once every minute. By the aid of the push-button switch S 4 manual resetting of the integrators can be accomplished at any desired time.

A rectilinear relationship, within $\pm 5\%$, is found between the deflection read from the recording paper and the known volume changes. The deflection for a given volume change is independent of the rate within a measured range from 5 to 150 strokes per minute. The phase shifting of the recorded flow rate in relation to the volume changes is less than 0.01 sec. Each galvanometer gives a rectilinear recording on the paper within a range of 45 mm. Baseline drift has always been less than 0.5 mm during the recording time used.

The main amplifier once electrically standardized allows the use of different sensitivities to obtain 1 mm deflections on the recording paper equal to 0.1, 0.2, 0.5, 1, 2 and 3 ml. Standardization has proved to give constant values during three years' use of the recording system. However, after each study a calibration with the syringe pump has been performed.

Flow rate is calibrated from the slope of a simultaneously recorded volume curve at points of maximal flow during inspiration and expiration.

The minute volume (\dot{V}) and frequency (f) are calibrated from the volume changes obtained by the syringe pump.

Intraesophageal pressure recording

The intraesophageal pressure changes are recorded by means of a polyethylene catheter, 1 mm inside diameter, introduced through the nose or the mouth (see Fig. 3). In conformity with the practice of McIlroy (7) and Cook *et al.* (2) in studying newborn infants, we have chosen to place the tip of the catheter between the upper and middle thirds of the esophagus. In full-term infants this is at about 10 cm from the lips. In some cases, the depth of the catheter has been controlled by chest roentgenograms. Two or three holes are made in the catheter's wall within 10 mm from the smoothed tip. The catheter is directly connected to an electromanometer (Elema, with the standard sensitivity), and the entire system is filled with physiological saline solution from an attached syringe and repeatedly flushed during the

determination. Due to the use of a liquid filled system and the high stiffness of the electromanometer's membrane (the modulus of volume elasticity = $0.07 \text{ mm}^3/10 \text{ cm H}_2\text{O}$)¹ the intraesophageal pressure changes are picked up with accuracy even when the esophageal mucosa touches the catheter holes.

After amplification the signals from the electromanometer are recorded on one channel of the Mingograph.

Reproducibility and calibration

After each study a pressure calibration is performed. In order to avoid interfering surface tension in the catheter holes, the catheter tip is placed near the bottom of a test tube, half filled with saline, and the whole system flushed. Different pressure changes can be recorded by moving the test tube up and down along a ruler.

There has always been a rectilinear relationship, within $\pm 5\%$, between the deflections read from the recording paper and corresponding known pressure changes. The base line drift has been less than 0.5 mm. At the sensitivities used, 1 mm deflection has been equal to 0.1, 0.2, 0.5, 1, 2, or 3 cm of water pressure.

Applications

The body *plethysmograph* is suitable for respiratory studies during steady conditions permitting determinations of tidal volume, frequency, minute volume and gas exchange in either well or sick infants. On fast-running recording paper the respiratory pattern can be studied as well as the mechanics of breathing by simultaneously recording the intraesophageal pressure changes. The apparatus has five outputs, but the four channels of the Mingograph are sufficient for our type of studies.

The "reverse *plethysmograph*" is especially suitable for short time recording of volume and intraesophageal pressure changes.

We will not comment on the use of the different values obtained in ventilatory

¹ The last standard model has a modulus of volume elasticity = $0.004 \text{ mm}^3/10 \text{ cm H}_2\text{O}$.

studies. However, a short review of the principles of analysis in mechanics of breathing and the different methods used for calculations may be of value, since this type of respiratory study in newborns is fairly new and not yet widely known.

Principles of analysis of the mechanical factors of respiration

Respiratory movements are based on two elastic systems, the lungs tending to decrease in volume and the surrounding thoracic cage tending to increase in volume. The two systems are connected to each other due to the cohesion that exists between the two wet layers of the pleura.

At the end of a normal expiration there is an equilibrium between the two elastic systems without any forces involved other than the elastic tension of each system opposing the other.

To produce an inspiration, i.e. increased inflation of the lungs, the respiratory muscles must be activated and move 1) the thoracic cage 2) the lungs and 3) the air in the air passages of the lungs and upper respiratory tract.

The main forces which have to be overcome are the following:

1) Change of elastic tensions:

a) Increase of the elastic tension of the lungs is related to the increasing expansion of the lungs, but independent of the velocity of this volume change.

b) As the elastic tension of the thorax is decreasing during inspiration, this "deficit" has to be compensated for by an increased effort of the respiratory muscles; the decrease of elastic tension in the thorax is thus actually acting as a force to be overcome.

c) *Friction* due to the respiratory movements:

a) Friction, due to *air flow*, between the gas molecules themselves, and between the air current and the walls of the respiratory tract is dependent on the anatomical condition of the air ways and on the air flow rate and the density of the ventilating gas.

b) Friction due to the *motion of non-elastic tissue* in the lungs and in the thoracic cage (including the diaphragm), is dependent on the quantity and quality of the tissues and the velocity of the motion.

3) *Cohesion* between the wet walls has to be overcome in certain conditions where collapsed parts of the respiratory tract are aerated during an inspiration. An "opening pressure" has to be built up before air movements will occur.

4) *Inertia forces* are very small and can be ignored.

At the end of the inspiration, as all movements have ceased, no friction is present. There is an equilibrium between the elastic tension of the lungs which has increased during inspiration and the sum of the contractile force of the respiratory muscles and the elastic tension of the thoracic cage, the latter having decreased during inspiration.

Expiration in quiet, normal breathing starts as soon as inspiratory muscles relax. The elastic elements of the lung, increasingly stretched during inspiration, now move back the lung and the thorax, decreasing their volume. Again frictional forces due to air flow and motion of non-elastic tissue have to be overcome, now having the opposite direction compared to inspiration. With decreasing expansion the elastic tension of the lungs will decrease while that of the thoracic cage will increase, and the expiratory movements

cease when equilibrium between the two is again reached. Thus, a respiratory cycle is completed.

In *studying the mechanics of breathing* the subject of main interest is in general the conditions *inside the lungs*.

Due to the ability of the connecting surfaces of the two systems to slip over each other and to the plasticity of the lung parenchyma, the resultant of the forces acting inside the lungs can be assumed to be acting evenly on the pleural surface of the lungs. This is counter-balanced by the resultant of the forces in the thoracic cage which is equal in magnitude but of opposite direction. Thus, these two resultants produce a negative pressure¹ in the virtual intrapleural space, the absolute amount of pressure being equal to each of them.

At the end of a normal expiration, when only the elastic forces are involved, this pressure is about -3 cm H_2O . During inspiration the forces balanced across the intrapleural space increase, the intrapleural pressure thus falling further below atmospheric pressure, i.e. becoming more negative. Due to the anatomical conditions the intrapleural pressure changes are reflected by similar pressure changes in the esophagus where they can easily be recorded.

Simultaneous recording of esophageal pressure changes and pulmonary volume changes permits the analysis of the mechanical factors involved during respiration.

¹ Since the atmospheric pressure acts equally on the outside of the thorax and in the lungs via the air passages it is considered as zero. Intrapleural pressure changes are considered as negative or positive in relation to atmospheric pressure.

Differentiation of elastic and frictional properties

An instructive, graphic method is to use *respiratory loops*, constructed from the pressure and volume curves.

At time intervals of, for example, 0.1 second, the corresponding values for changes of pressure and volume in relation to the values at the end of the expiration, ΔP and ΔV , are plotted on a graph (see Fig. 6) with pressure in cm water on the abscissa and volume in ml on the ordinate. In addition, points of no flow,—i.e. the end of inspiration and expiration,—are especially plotted. All these points are consecutively connected with straight lines.

The inspiratory part (OIA) of this ΔV - ΔP relationship curve starts at the zero point, and ends at a top point of the V-axis. From this point the expiratory part (AEO) of the curve returns to zero, completing the figure of a loop. The shape of the loop is somewhat uneven due to the technic of constructing it at certain time intervals and because of the interference of heartbeats in intraesophageal pressure.

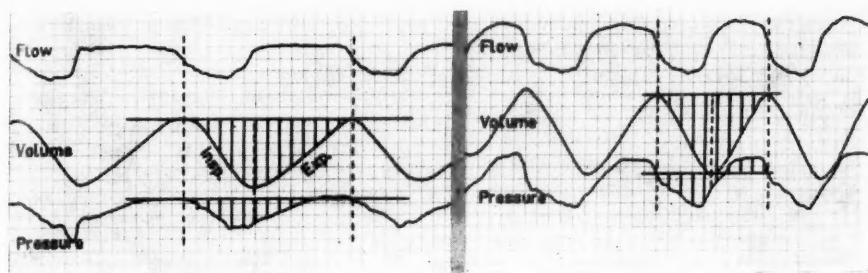
At the end of inspiration and of expiration there is no flow, and thus no frictional forces are present. The pressure difference between these two points (ΔP) represents the increase of elastic tension due to the increased expansion (ΔV) of the lung during inspiration, i.e. the tidal volume of the actual

breath. The ratio $\frac{\Delta V}{\Delta P}$ is approximately constant for different breaths in each individual within normal breathing range, telling how "compliant" that individual's lungs are according to a certain pressure change. This ratio is termed *lung compliance* and is expressed in the units of ml/cm H_2O . The inverse ratio,

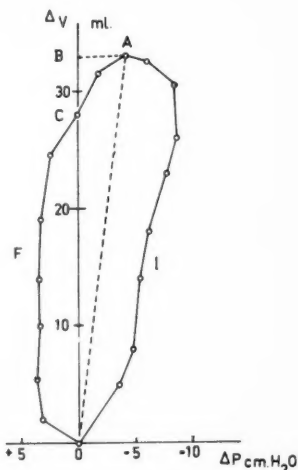
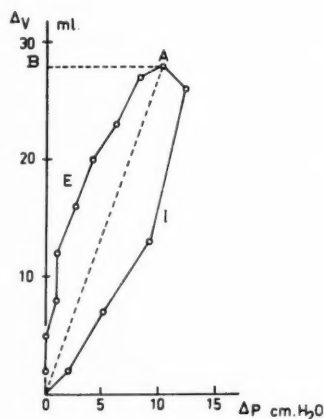
$$\frac{\Delta P}{\Delta V} \text{ expressed in cm } H_2O/\text{ml}$$

volume change has been called *elastance*.

A rectilinear relationship between elastic tension and expansion of the lung has been found within the range of normal quiet



a.



b.

Fig. 6. Graphical construction of respiratory loop (with the "compliance" line marked as a dotted line). To the left: normal breath with passive expiration. To the right: breath with active expiration.

breathing; thus a straight line may be drawn between the two points of no flow in the loop.

This "compliance line" represents the pressure-volume relationship of an ideally elastic system, i.e. without frictional forces involved. Actually there is friction due to air-flow and motion of non-elastic tissue in the lungs. These will be considered together under the term "pulmonary friction".¹ To

¹ By the technic used friction due to air-flow cannot be differentiated from friction due to motion of non-elastic tissue in the lungs. Of the two, however, air-flow friction is of greater magnitude.

overcome pulmonary friction during inspiration the pressure gradient at each moment must be higher than indicated by the "compliance line". This requires a pressure (P_{Ir}), which has to be added to the pressure required to overcome the increase of elastic tension of the lungs at the same moment (P_{El}) as shown by the "compliance line". During expiration, when the increased elastic tension of the lungs is liberated and is the instigator of the expiratory movements in normal quiet breathing, the pressure used to overcome the pulmonary friction (P_{Er}) is in opposition to and at each moment has to

be subtracted from the pressure representing the elastic tension of the lungs as shown by the "compliance line" (P_{Eel}):

Thus: $P_{Iel} + P_{Ifr} = \Delta P_I$ = the recorded pressure change at any moment of inspiration

$P_{Eel} - P_{Efr} = \Delta P_E$ = the recorded pressure change at any moment of expiration

Being related to the flow rate (volume change per unit of time = $\Delta V/t$), the pulmonary friction will be greatest at about the middle third of inspiration and expiration when flow is highest. Therefore the respiratory loop will be broadest at about the middle with the respiratory loop in a normal breath thus approaching the shape of an ellipse.

Since in quiet normal breathing the air flow in the respiratory tract is mainly laminar, the relationship between pulmonary friction and flow rate can be considered

rectilinear. Thus the ratio $\frac{P_{fr}}{\Delta V/t}$ in normal

quiet breathing will be constant in each individual throughout a single respiratory cycle as well as for different breaths. The ratio is a *resistance* in conformity with Ohm's law and expressed as cm H_2O /lit/sec. It has been called the pulmonary flow resistance, the air flow resistance, the airway resistance or only flow resistance or resistance. We use the term *pulmonary flow resistance*. The inverse ratio

$\frac{\Delta V/t}{P_{fr}}$ in lit/sec/cm H_2O tells how

"conductive" the airways are and is called *conductance*.

The elastic as well as the frictional factors can be evaluated visually from the shape of the respiratory loop. We have found the respiratory loops very useful in understanding and evaluating the mechanics of breathing, especially in the first minutes of life when respiration is seldom quiet and regular.

In regular quiet breathing mechanical properties may be sufficiently characterized by the compliance and pulmonary flow

resistance¹ alone, which can be calculated directly from the curves of pressure and volume changes and flow rate (see Fig. 7).

Compliance is the ratio of volume change to the change in intraesophageal pressure measured between points of no flow, when $\Delta V = V_T$ and $\Delta P = P_{el}$.

Pulmonary flow resistance is calculated according to Mead (9) as the ratio of pressure difference ($\Delta P_I - \Delta P_E$) to the corresponding total flow change ($\Delta V_I/t + \Delta V_E/t$) between points of equal volume. At these two points P_{Iel} is equal to P_{Eel} , being on the same point of the "compliance line", and ($\Delta P_I - \Delta P_E$) will give ($P_{Ifr} + P_{Efr}$). If no flow curve is available total flow change can be measured from the slopes of the volume curve at these two points. Pulmonary flow resistance thus calculated will give a mean value for inspiration and expiration which is approaching but not identical with the arithmetical mean of inspiratory and expiratory pulmonary flow resistance. To be able to differentiate between inspiratory and expiratory pulmonary flow resistance, it is necessary to differentiate between P_{el} and P_{fr} . When simultaneous recordings of flow rate, volume change and pressure change are available, a simple graphical method has been used (see Fig. 7):

The three points of no flow in one breath (end of previous expiration, end of inspiration and end of expiration) are marked on the flow rate, volume and pressure curves. In each curve these three points are connected by dashed lines. Due to the S-shape of the volume curve, the connecting lines will cross the volume curve during inspiration and expiration. The points corresponding in time on the connecting lines of the pressure curve will represent the P_{Iel} and P_{Eel} respectively at these two moments, and the difference of pressure from recorded pressures

¹ Elastance and conductance can, of course, be used as well. It may seem to be more logical to use conductance in connection with compliance, since both show an effect per unit of pressure change. However, in clinical practice pulmonary flow resistance is most frequently used together with compliance.

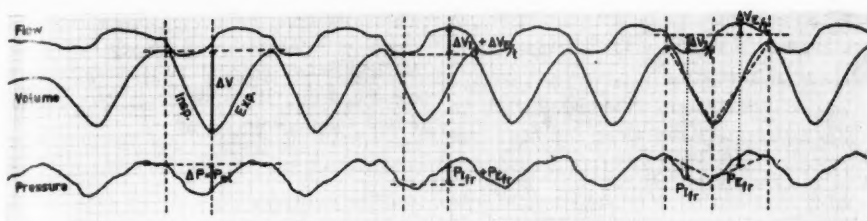


Fig. 7. Mechanical properties of the lungs directly calculated from the record.

Elastic properties:		Frictional properties:	Calculated according to Mead	Calculated for insp. and exp. [see text]
Compliance: $\frac{\Delta V}{P_{el}}$ ml/cmH ₂ O	Pulm. flow resistance: $\frac{P_{fr}}{\Delta V/t}$ cmH ₂ O/lit./sec.		$\frac{P_{Ifr} + P_{Efr}}{\Delta V_{I/t} + \Delta V_{E/t}}$	$\frac{P_{Ifr}}{\Delta V_{I/t}}; \frac{P_{Efr}}{\Delta V_{E/t}}$
Elastance: $\frac{P_{el}}{\Delta P}$ cmH ₂ O/ml	Conductance: $\frac{\Delta V/t}{P_{fr}}$ lit./sec./cmH ₂ O		$\frac{\Delta V_{I/t} + \Delta V_{E/t}}{P_{Ifr} + P_{Efr}}$	$\frac{\Delta V_{I/t}}{P_{Ifr}}; \frac{\Delta V_{E/t}}{P_{Efr}}$

will be P_{Ifr} and P_{Efr} respectively which can be shown trigonometrically. Corresponding flow rate ($\Delta V_{I/t}$ and $\Delta V_{E/t}$) necessary for the calculation of the respective pulmonary flow resistances, is measured from the flow rate curve. The flow rates at these two points of the respiratory cycle, independent of the respiratory pattern within wide range, have been found usually to coincide with the maximal flow rate during inspiration and expiration.

The use of an *oscilloscope* with two coordinates for recording simplifies the determinations. By feeding into the oscilloscope the outputs of the amplifier-recorder systems for volume and pressure change (ΔV and ΔP) onto the ordinate and abscissa respectively, respiratory loops are obtained directly on the screen. The mean angle between the abscissa and imagined "compliance lines" of a series of consecutive breaths can be estimated by means of a protractor on the oscilloscope. From the tangent of this angle the compliance is easily calculated. Also the relationship between flow rate ($\Delta V/t$) and pressure used to overcome the pulmonary friction (P_{fr}) can be read directly from the scope according to Mead *et al.* (8). Instead of volume change, flow rate ($\Delta V/t$) is now

recorded on the ordinate of the scope. On the pressure change record (ΔP) a 180 degree phase-shifted (= "inverted") volume change record is superimposed. The amplification of this volume change record is so adjusted, without influence on the flow rate recording, that the loop of the oscilloscope is replaced by a line tracing. This means that the magnitudes of the superimposed tidal volumes are equal to the pressure changes between points of no flow, eliminating the P_{el} from the pressure recording, thus only the P_{fr} being recorded. When this relationship is rectilinear there is a laminar air flow in the respiratory tract. The mean angle between the ordinate and these lines of a series of consecutive breaths is read from the protractor. From the tangent of this angle the pulmonary flow resistance ($P_{fr}/\Delta V/t$) is calculated easily.

Calculations of respiratory work

Compliance and pulmonary flow resistance are mechanical characteristics of an individual's lungs. Their functional influence can be evaluated by calculating the respiratory work per single breath or per unit of time.

The respiratory loop can be used for estimating work done in accomplishing a breath:

Since Work = Force \times Distance

= Pressure \times Volume (for a volume system)

$$\text{i.e.} \quad \begin{aligned} \Delta V &= V_T \int P \cdot \Delta V \\ \Delta V &= 0 \end{aligned}$$

The work done for overcoming mechanical forces in the lungs during a single breath can be integrated graphically from the loop areas (see Fig. 6) and differentiated into different components:

During	Loop area	Corresponding to work done for overcoming:	Done by
Inspiration	{ OAB OIA	increase of elastic tension of the lungs pulmonary friction	} respiratory muscles
Expiration, passive	{ OAE OEAB	pulmonary friction forces in the thoracic cage ¹	{ potential energy stored during inspiration in increased elastic tension of the lungs
Expiration, forced	{ ABC OACF { OAC OCF }	part of forces in the thoracic cage ¹ pulmonary friction	{ stored elastic potential energy (see above) respiratory muscles

¹ Area OEAB corresponds to that part of work done to overcome the increase of elastic tension of the lungs during inspiration (and stored as potential energy) that is not used up in the lungs during expiration. Actually this work cannot be "gained" but must be assumed to be dissipated when the thoracic cage is in motion.

Total work required by the lungs for a breath with *passive* expiration will correspond to the area OIAB (equal to the inspiratory work only). During a *forced* expiration when interpleural pressure is driven up by active contraction of respiratory muscles above the value found at the end of a normal quiet respiration, the expiratory part of the loop will extend over to the positive side of the abscissa (zero being set at the pressure value at the end of a normal expiration). The area OCF will correspond to active work required for the expiration done by the respiratory muscles (see Fig. 6). Total work required by the lungs for a breath with forced expiration will thus correspond to the area OIABCF.

Total work can be directly approximated from the mechanical and ventilatory values in so far as breathing is regular:

1) according to Mellroy (6) from the total pressure change in cm H₂O during a respiratory cycle (P) and the minute volume (V):

$$\text{Work (in gm-cm per minute)} = 0.6 P\dot{V}$$

2) using the formula of Otis, Fenn and Rahn (11) from the determined elastic (elastance) and frictional (pulmonary flow resistance) factors, tidal volume and respiratory rate.

Both formulas have been shown by Cook *et al.* (2) to apply even for infants in quiet regular breathing.

The purpose of outlining the methods of analysis in mechanics of breathing has been to introduce the background for methods used in the respiratory studies in newborns which will be published later in this journal. For a more detailed discussion of this subject the reader is referred to the rapidly growing literature in this field comprising mainly investigations in adults (3, 6, 9, 10, 11, 13). However, only a few studies have been published up to now dealing with investigations in newborns (1, 2, 5, 7).

Summary

Apparatus and methods for studying the pulmonary ventilation and the mechanics of breathing in newborn infants are described. For volume recording with long duration a body plethysmograph system is used; for short recording periods, a reverse plethysmograph system. For studies of the mechanics of breathing the intraesophageal pressure changes have been

recorded simultaneously with the volume changes occurring during single respiratory cycles. The reproducibility and calibration of the methods are explained. The setup has been used in respiratory studies in the neonatal period, which will be published at a later date in this journal.

An outline of the principles of analysis of the mechanics of breathing and the different methods used for calculations are given.

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On the Problem of Congenital Hemopathies (Congenital Myeloid and Erythremic Blood Picture)

by J. BJURE, K.-E. FICHTELIUS and S. RANSTRÖM

According to Kelsey & Anderson (4), a diagnosis of congenital myeloid leukemia requires that manifestations shall be present at birth or at most a day or two thereafter; that the liver, spleen and lymph nodes shall be enlarged; that the blood picture shall exhibit a high number of leukocytes, with predominantly immature forms; and also that there shall be no evidence suggesting the presence of erythroblastosis, syphilis or sepsis. At autopsy a greater number of extramedullary myeloid infiltrations shall be found than reasonably could have been formed after parturition.

As judged by these criteria, a good deal of the published cases of congenital myeloid leukemia must be disqualified, particularly those in the earlier literature. The chief basis for rejection would be too late an onset, but the fact that erythroblastosis would have been a more likely diagnosis is also cause for exclusion. Even when cases of this type have been eliminated, some doubt has been expressed as to which of those that remain can be accepted as instances of genuine congenital myeloid leukemia and which cannot. Thus, having critically reviewed the literature,

Burgstedt & Hartl (2) approved as few as 11 cases. However, in our opinion, Smith's case (11) should be deleted from the list of "Definitive Cases" because symptoms only began at the age of 3 weeks. Also, we find it more or less evident that the case described by Söderhjelm & Ranström (13) ought to be on this list. Then there is a group of 7 cases diagnosed as congenital leukemia + mongolism. Söderhjelm & Ranström's case (13) similarly exhibited superficial signs of mongolism, although the diagnosis could not be verified at autopsy. While Krivit & Good (6) claimed that mongolism is associated with leukemia of childhood oftener than if the combination were random, Sutow (12) maintained that the incidence of mongoloid signs was no higher in leukemias than in the population at large.

Erythremia, a disease closely akin to myeloid leukemia and first described by di Guglielmo (3), is characterized by a cryptogenic hyperplasia of the erythropoietic system analogous to the myeloid hyperplasia accompanying leukemia. Of the 80 cases or so included in the literature under this diagnosis, Moeschlin (9), for example, would accept but 5 as true in-

stances of di Guglielmo's disease. Moreover, the alleged cases of congenital erythremia have without exception turned out to be cases of erythroblastosis (the latter diagnosis, incidentally, is given in the subtitles to the publications). Accordingly no instance of genuinely congenital erythremia has yet been reported.

Two cases of congenital hemopathy will be presented in the following report which clinically and pathologically resembled one another in some respects and differed in others.

Case Reports

Case 1

A girl born on Feb. 6, 1957 (Göteborg, Record No. 318/57) to a para III 30 year old mother whose 2 previous children were in good health. As the mother was an adopted child without knowledge of her family, no hereditary information was available on the maternal side. In the father's branch of the family there seemed to be no blood disorders. During pregnancy the mother had a slight anemia with a minimum Hb reading of 10.3 g %, and during the last month,—(Apart from this she was normal),—traces of albumin were found in her urine. The mother stated that the fetal movements had been normal, that is vigorous and frequent, until 3 weeks before delivery when they became rather infrequent and weak. Parturition took place at term and was uncomplicated. The child weighed 4050 g at birth.

Immediately at birth the child's entire integument was purpuric and showed numerous tumours of varying size, the largest having a diameter of approximately 3 cm (Fig. 1). Punctate hemorrhages were observed in the conjunctival and oropharyngeal mucous membranes. In due course additional evidence of the hemorrhagic tendency became apparent in the form of hematuria, hematemesis and melena. From the very

beginning the child was weak: it cried faintly and had a somewhat accelerated respiratory pattern. In the course of subsequent days, the child's condition underwent a gradual deterioration, with increasing apathy, dyspnea and,—as from the 4th day,—hyperpyrexia with fever peaks rising close to 39°C. The intracutaneous hemorrhages and infiltrations paled and grew slightly smaller. On the 4th day, too, many rales were heard over the lungs, and the previously non-palpable liver was now distinctly felt about 3 fingers below the right costal arch. The spleen and lymph nodes were not palpably enlarged. On the 6th day the child's condition became still worse and on the 7th day she died.

The blood picture varied in the following manner.

Day of life	1	2	3	4	5	6	7
Hb g %	15.0		14.8				10.9
RBC (millions)	3.7		4.3				2.7
WBC (thousands)	66		35		91	156	150
Platelets (1000)		32			55		

Differential blood count: staff forms, 1.5 %; segmented forms, 2 %; lymphocytes 31 %; monocytoid reticulum cells, 65 %; 24 nucleated RBC to 200 WBC (approximately the same proportions found in subsequent counts).

Other Laboratory Findings. Clotting time, 5 min; bleeding time, 22.5 min; prothrombin index, 60 and 75; reticulocytes, 2.6 %. Bilirubin, 11.1 mg % maximum. Total proteins, 5.6 g %. Osmotic resistance—incipient hemolysis, 0.45 % NaCl; complete hemolysis, 0.20 %. Albuminuria and microscopic hematuria. WR neg.

Blood Serum Studies. The mother belonged to group A Rh (+), type CDe-cde. No irregular antibodies could be demonstrated in the mother's serum and the Coombs' test was negative even when the child's blood corpuscles were used for testing. The child's blood belonged to group A Rh

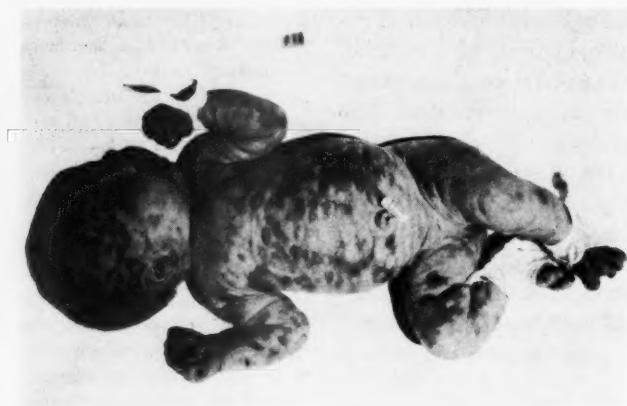


Fig. 1. Purpura and multiple tumours of the skin.

(—), type cde-cde, and its blood serum was negative on direct Coombs' testing. Examination of a puncture specimen of tibial marrow obtained a few hours before death on the 7th day revealed a markedly suppressed erythropoiesis of normoblastic character, slight anisopoikilocytosis and no particular hypochromasia. Two dissimilar types of cell were dominant. One was a fairly large, round to ovoid cell with a slightly irregular outline and a round to ovoid nucleus presenting a coarse chromatin pattern and containing 4 to 5 nucleoli; its protoplasm showed weak basophilia with acidophilic streaks. The other variety of cells were larger with larger nuclei and a more strongly basophilic protoplasm without acidophilic streaks. These cells constituted pre-stages to true reticulum cells and were found to be peroxidase negative.

Autopsy. In the skin there were a number of at most walnut-sized tumours which had a greyish white cut surface and lacked distinct demarcations with the surroundings. The *pericardium* contained a small amount of sanguinous fluid and disclosed an abundance of subpericardial hemorrhages. The *heart* was of normal size, with no malformations. In the *pleura cavities* there were small amounts of sanguinous fluid and subpleurally were found fairly copious hemorrhages.

The *lungs* exhibited some scattered parenchymatous hemorrhages but no other lesions. Purulent material was found in the *trachea* and some of the larger *bronchi*. The *kidneys* were slightly enlarged, and in the *pelvis*, *ureters* and *bladder* many mucosal hemorrhages were encountered. The *genitalia* were normal. Except for an abundance of mucosal hemorrhages the *digestive tract* presented no abnormalities. The *spleen* and *thymus* seemed more or less unchanged. The *lymph nodes* were often up to pea-size in the mesentery but presented no abnormalities elsewhere. The *liver* was enlarged (weight, 195 g). The *pancreas* showed conspicuous enlargement and was 3 to 4 times the usual size. The *meninges* showed no hemorrhages and the *tentorium* was unbroken. The *cerebral parenchyma* exhibited a normal appearance without signs of kernicterus.

Microscopic Examination. *Skeleton and bone marrow* (Fig. 2). The bone structure was of the usual type and showed no signs of either osteosclerosis or osteoporosis. The normal hemopoietic structures were almost completely replaced by a tissue with a high density of polygonal reticulum cells exhibiting marked polymorphism and a moderate number of mitoses (Fig. 2b). These cells were devoid of fatty substances. The small

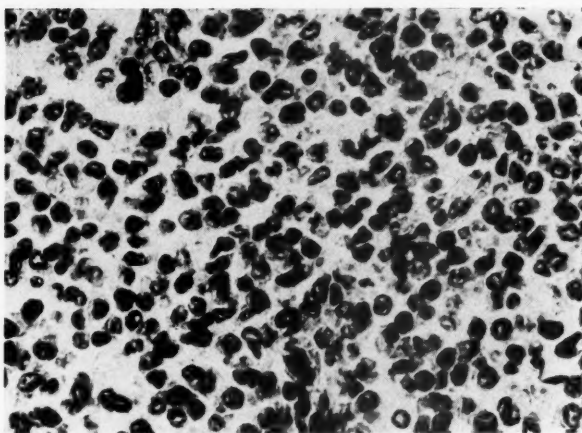


Fig. 2. Bone marrow replaced by an atypical reticulum cell tumour tissue; only some few erythropoietic cells, no myelocytes.

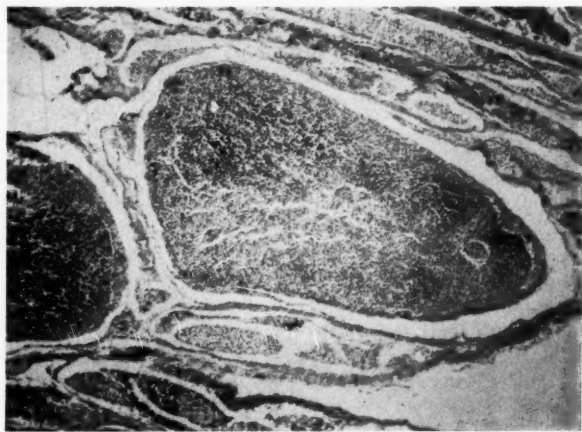


Fig. 3. Lymph nodes with the lymphoid tissue subtotally replaced by reticulum cell tumour tissue, also periglandular infiltrations.

amounts of the residual erythropoietic system was on the whole normal in appearance, apart from polyploidism of occasional normoblasts. The megakaryocytes had disappeared almost completely. Of the myelopoietic elements one could see merely occasional widely scattered myelocytes, the majority of them being eosinophilic. Whereas no distinctive myeloblasts were encountered,

some of the reticular cells were more basophilic than most and consequently could be regarded as stages intermediate between reticulum cells and myeloblasts.

Lymph nodes (Fig. 3). The normal lymphoglandular structure was wholly or almost completely eradicated and replaced by a tumorous tissue with the same features as the reticulum cell tissue in the bone marrow.

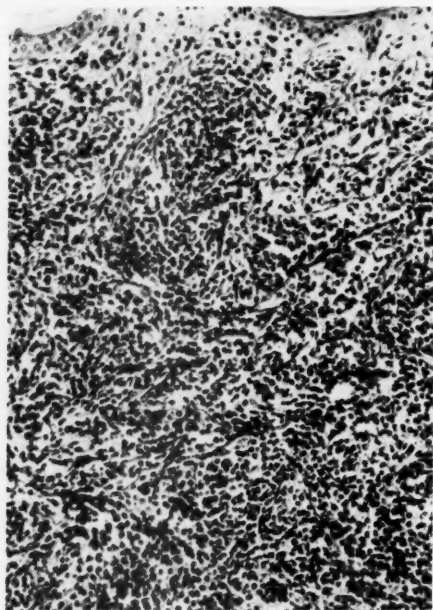


Fig. 4. Skin focus with massive infiltration of tumour tissue.

Periglandular infiltrations of similar tissue were also encountered.

Skin (Fig. 4). Large and small focal tumours consisting of the aforementioned reticulum cell tissue were encountered, the infiltration being massive in the corium but gradually diminishing with depth in the subcutaneous layer.

Liver. Many portal tracts were invaded by the same type of reticulum cells, but nowhere in quantity. Fine droplets of fatty substance were sparsely but uniformly distributed throughout the liver cells. No iron pigmentation was noted.

Spleen. The Malpighian nodules showed atrophy, the red pulp exhibited diffuse and rather copious reticulum cell proliferation, and there was no appreciable erythropoietic or myelopoietic activity.

Thymus. Contained scattered Hassal's corpuscles but no necrosis, the reticulum cell tissue had replaced part of the lymphoid tissue.

Lungs. The alveolar septa showed generalized, moderate thickening owing to reticulum cell infiltration. Signs of hemopoietic activity, or pneumonial lesions or peripheral bronchitis were not encountered.

Pancreas (Fig. 5). Very considerable accumulations of reticulum cell tumour tissue were seen both interlobularly and intralobularly, the infiltration proceeding into the neighbouring tissues, not only fat and regional lymph nodes but also adjacent nerve trunks being involved.

Kidneys. The cortex and pyramids as well as the pelvic mucosa were diffusely and in parts profusely invaded by the reticulum cell tissue.

Myocardium. A few thin strings of reticulum cells were found along the myocardial vessels. The endocardium and pericardium lacked signs of similar infiltration.

Pituitary. The cellular composition of the organ was compatible with the subject's age and showed no invading foreign cells.

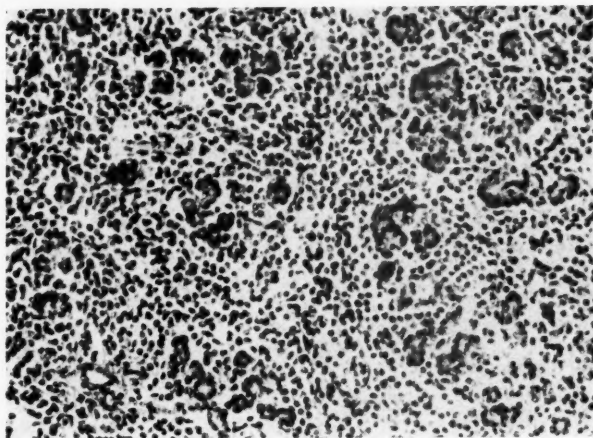


Fig. 5. Scattered pancreatic tubules in the reticulum cell tumour tissue.

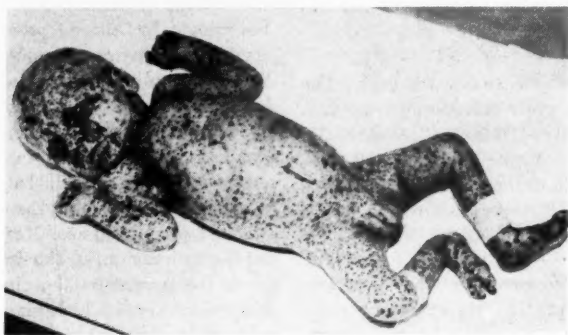


Fig. 6. Generalized purpura.

Thyroid. The appearance of the follicles was normal and the gland was free from infiltrations.

Case 2

A boy born on April 17, 1954 (Upsala Pediatric Clinic, Record No. 414/54). Apart from the fact that the paternal grandmother had pernicious anemia, nothing was known about any familial occurrence of blood diseases. The mother had been in good health during pregnancy except for a few days 2 weeks before delivery, when she ran a high temperature, was exhausted and had head-

ache and "aches throughout the body". Parturition occurred at term and was uneventful, the child weighing 3320 g. Immediately at birth the boy exhibited generalized cutaneous purpura with the discrete, in parts confluent infiltrations measuring about 3 mm in diameter (Fig. 6). The liver was palpated one finger below the costal arch and the spleen immediately beneath it. The boy became increasingly apathetic during the first days of life. The intradermal hemorrhages dried up and turned crust-like. On the 3rd day a blood transfusion was given. On the 4th day the boy's temperature rose over 39°C , he became

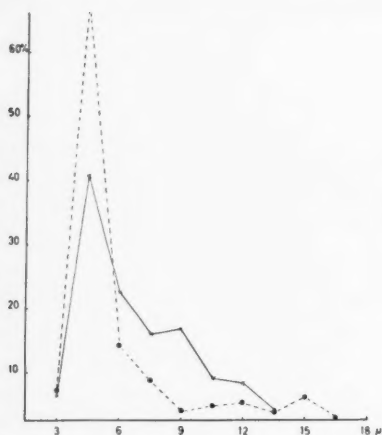


Fig. 7. Nuclear diameter distribution of erythropoietic cells in the bone marrow punctates on the 5th day and immediately post mortem (dotted line).

dehydrated and began to cry wailingly. The liver and spleen grew considerably in size. The boy was given fluids subcutaneously, antibiotics and—during the last days—cortisone, all without much benefit. The boy's general condition deteriorated progressively, and on the 7th day he died.

Laboratory Investigations. Blood picture:

Day of Life	1	2	3	4	5	6
Hb g (%)	13.7	14.1	17.7	17.2	15.1	15.1
RBC (millions)	4.0	4.0	4.2	5.3	4.3	4.5
WBC (thousands)	34	9	15.1	14.6	14.6	11.8
Platelets (thousands)	26	15	22	21	24	24
Nucleated RBC (thousands)	56	50.4			69.9	

Differential count: A few per cent myelocytes and metamyelocytes, occasional reticulum cells. Anisocytosis, macrocytosis, poikilocytosis, polychromasia, also very immature forms, polyploidism and other forms of karyotypia were observed.

Other Laboratory Findings. Total proteins, 4.1 g %; albumin-globulin quotient,

0.7; fibrinogen, 0.2 g %. Clot retraction—after 3 hours, 15 % serum; after 8 hours, 36 % serum. Vitamin B₁₂ content of serum, 1.6 and 1.3 gamma/ml. Hanger's reaction, + + +. Serum iron, 262 gamma %. Total lipids, 650 mg %. Bleeding time, clotting time and osmotic resistance, normal. Urinary sediment, nil; no albuminuria or glucosuria. WR and blood culture, negative. The child's blood belonged to group A Rh (+), direct Coombs' test was negative and no irregular antibodies could be demonstrated in the mother's serum.

On the fifth day and immediately after death puncture specimens of tibial marrow were obtained which revealed the following characteristics. The erythropoiesis was absolutely dominant, the myelopoiesis being markedly suppressed but of normal type; there were extremely few megakaryocytes. Pathologically altered proerythroblasts and erythroblasts were encountered, some of them resembling promegaloblasts and megaloblasts respectively. A high percentage of the oxyphilic erythroblasts exhibited polyploidism, with up to as many as 5 nuclei of different sizes per cell. In the postmortem specimen oxyphilic erythroblasts showed a marked predominance. Measurement of the nuclear diameter in the erythroid cells of these bone marrow specimens have been plotted in Fig. 7 which gives the percentage of cells in different diameter classes. Inspection of the nuclear diameter distribution thus reveals that there was a slight excess of small erythroblast nuclei on the 5th day (cf. Weicher). These small erythroblast nuclei with a diameter of about 4.5 μ were still more overrepresented in the post mortem specimen. The appearance in the latter specimen of some proerythroblasts with large nuclei should also be noted.

Autopsy. The skin over the entire body was covered with dark reddish brown crust-like formations several mm in diameter. Here and there the crusts were coalescent and formed larger areas. The skin between the crusts was moderately jaundiced. No external deformities were seen. Generalized jaundice of organs and tissues was present.

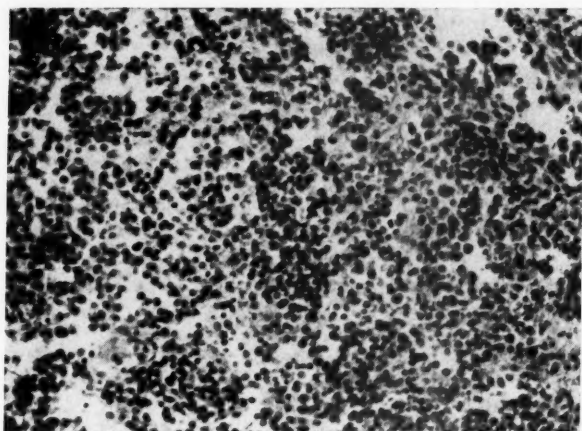


Fig. 8. Bone marrow with foci of dark staining erythropoietic cells in different stages of maturation; diffusely scattered myelopoietic cells of normal appearance, abundance of large and atypical reticulum cells partly forming tumorous infiltrations.

The meninges lacked hemorrhages and the tentorium was unbroken. The cerebral parenchyma looked normal, no kernicterus. The heart was of normal size; the foramen ovale was patent but valvate; the Botallian duct admitted a probe; the large vessels showed no abnormalities. The lungs were hypostatic and exhibited some atelectases. The mucosa of the digestive tract was normal apart from a few minor intramucosal hemorrhages in the oral cavity. The liver was enlarged, weighing 165 g, smooth externally and showed a dark reddish brown surface on section. The pancreas had a normal appearance. The urogenital organs showed no abnormalities. The skeleton exhibited no gross lesions; radiographic examination of the femur showed a normal bone structure without osteosclerosis or osteoporosis. A few, at most pea-sized, lymph nodes were encountered in the mesentery and para-aortally but there was no question of generalized lymphoglandular enlargement. The spleen was enlarged, weighed 41.5 g and had a dark red parenchyma. The thymus weighed 5.5 g, was fibrotic and contained a few small necrotic foci. The thyroid and adrenals (9.5 g) were of normal appearance.

Microscopic Examination. Skeleton and

bone marrow (Fig. 8). The bony structure was of the normal type without signs of osteosclerosis. In the marrow spaces there was a tissue rich in cells, predominantly reticulum cells of polymorphic appearance some of which were in a mitotic state. The normal hemopoietic apparatus, some of which had yielded place to this reticulum cell tissue, was composed almost exclusively of atypical erythropoietic elements. There were only a few basophilic and polychromic erythroblasts but on the other hand the eosinophilic erythroblasts with an atypical, often segmented nucleus were most abundant. With respect to leukopoietic elements, all one could see was a few myelocytes, no distinct myeloblasts and practically no cell forms of greater maturity whatsoever. The megakaryocytes were few and small. No iron-staining substance was discerned.

Lymph nodes (Fig. 9). The normal lymphoglandular features were obliterated, so that only an indicated marginal sinus and a few small scattered lymphocyte accumulations were encountered in a compact tissue of tumorous appearance which was rich in markedly polymorphic reticulum cells some of which were in a mitotic state. Here there was no semblance of either erythro-

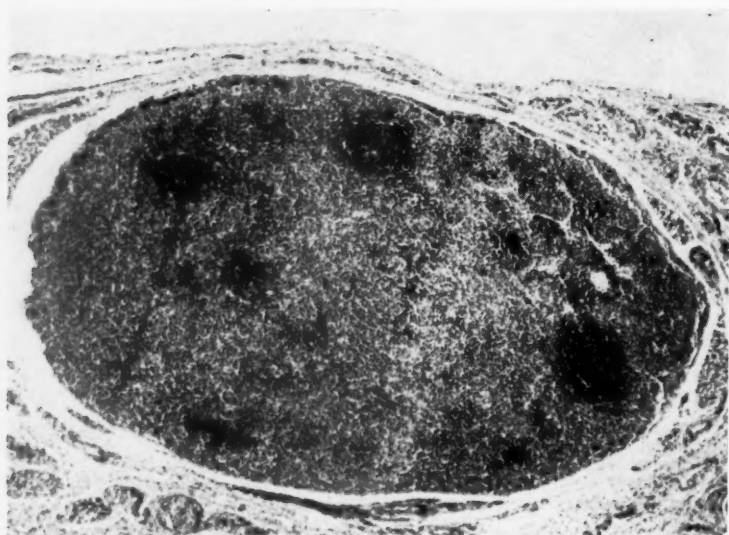


Fig. 9. Lymph node with small foci of residual lymphoid tissue most of which is replaced by atypical reticulum cell tumour tissue.

poiesis or leukopoiesis, and iron-staining substance was completely absent.

Liver. This organ exhibited an abundance of biliary thrombi, and between the columns of liver cells a generalized but mild increase in connective tissue had occurred. There was no fatty degeneration and no necrosis. Small amounts of iron pigment and small, scattered foci of atypical erythropoietic activity of the same type as in the bone marrow, were seen, with no manifestations of leukopoiesis and no megakaryocytes.

Spleen. The structure of the blood-engorged parenchyma was on the whole preserved but the Malpighian nodules were atrophic; a fairly marked, atypical reticulum cell proliferation was noted in the red pulp. Some small foci of the aforementioned atypical erythropoietic elements were seen scattered diffusely throughout the organ; occasional myelocytes were all that was encountered of the leukopoietic apparatus. Only solitary, small megakaryocytes were seen and there was practically no iron-staining substance.

Thymus. The normal parenchyma had been entirely lost and replaced by tumour tissue lobed by fibrous cords and consisting of polymorphic reticulum cells. Most parts contained small and large detritus foci undergoing incipient calcification as well as a number of minor parenchymatous hemorrhages. Neither erythropoietic nor leukopoietic activity was manifest, and there were no traces of iron-staining substance.

Lungs. In most parts of the alveolar septa, the majority being thickened, there were small focal accumulations of the same atypical erythropoietic elements as elsewhere. Also encountered were extensive regions of atelectasis and stasis, residues of hyaline membranes in the alveolar ducts, and small, scattered, lesions of acute pneumonia with neutrophilic leukocytes.

Kidneys. No abnormalities were recorded.

Pituitary. For the age level concerned, there was a slight increase of eosinophils, some deficiency of basophils but no invading cellular elements. Otherwise the endocrine organs were entirely normal.

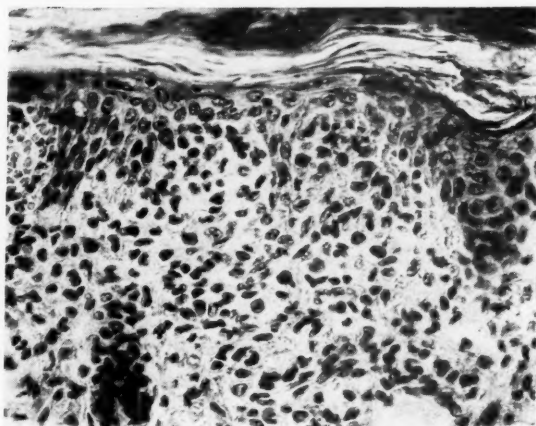


Fig. 10. Skin with tumorous infiltration of atypical reticulum cells.

Skin (Fig. 10). Foci of atypical, tumorous, reticulocellular tissue were encountered subepidermally in the corium, with minor hemorrhages or their residuals in the vicinity. The epidermis bordering on these foci was thinner than usual and acanthotic. Most parts, but not all, of the corneal layer overlying these foci had merged with crusted formations containing old blood. Erythropoietic cells were sparsely represented in the neighbourhood of the foci. Neither the cutis nor subcutis showed any inflammatory reaction.

Comments

That the hemopathic conditions described in the foregoing were congenital cannot be doubted. It will be realized that these two cases have some common features, from a clinical as well as histological point of view; thrombopenia with a hemorrhagic diathesis, anemia, jaundice, tumour infiltrations in the skin, hepatomegaly, fever and, morphologically, an extensive proliferation of reticulum cell elements of distinctly tumorous character, particularly in the bone marrow, lymph nodes

and skin. The two cases differed chiefly with respect to the blood picture, which in Case 1 presented all the features of a highly immature myeloid leukemia and in Case 2 was characteristic of atypical erythropoiesis leaving the myelopoiesis virtually unaffected. The important question posed by these two cases, and raised by any case of a leukemic blood picture during the neonatal period, can be put as follows. Should the clinical and morphological abnormalities observed in the reticuloendothelium including the hemopoietic apparatus be considered reactive, that is secondary to some demonstrable basic disorder, or should they be regarded as neoplastic and hence cryptogenetic or "primary"?

In both the cases reported here erythroblastosis and syphilis can be ruled out as etiological factors; indeed, the morphological changes observed in these two cases are completely different from those associated with either of the latter disorders.

It has been pointed out that an infec-

tion might be capable of inducing considerable proliferation in the reticuloendothelial system including the hemopoietic apparatus (1, 5). But such a proliferation has apparently never been described as tumorous. That an infection can serve as a triggering factor for a leukemoid reaction in the peripheral blood is well known; but there is nothing in the literature suggesting that an infection in human beings would, in addition, be capable of inducing a reticuloendothelial proliferation massive and atypical enough to be morphologically distinctly tumorous. On the contrary, all experience indicates that such is not the case. Here it suffices to mention that a generalized infection as severe as congenital syphilis never gives rise to such a proliferation. The same applies, in our experience, to cases of other severe congenital infections (e.g. pneumonia, pleural empyema). Moreover, in none of Smith & Coworkers' comprehensive series of septic cases during the neonatal period did any reticulocellular proliferation take place. Indeed, not even a leukemoid blood picture was seen. Leukocytosis occurred only in conjunction with staphylococcal and streptococcal infections, whilst coli infections were accompanied by normal or depressed leukocyte counts. The latter authors expressed the opinion that during the neonatal period sepsis can be diagnosed reliably only following a blood culture. This was negative in Case 2 and was unfortunately not carried out in Case 1. In Case 2 the mother showed signs, for a few days 2 weeks before parturition, of an acute rapidly abating infection, possibly of the influenzal type. It appears improbable (but perhaps not entirely impossible) that this infection would have in-

duced sepsis in the fetus without its expiring in utero or without labour commencing during or immediately after the infection. Incidentally, it seems safe to assume that in a subject whose reticuloendothelium is so profoundly altered as in the two cases described above even a mild infection might readily lead to sepsis which then would be the immediate cause of death without being the primary factor in the disease complex.

All things considered, therefore, it seems most unlikely that an infection could have been the causative factor for the excessive and atypical reticuloendothelial proliferation seen in the cases reported here. Moreover, in these cases the proliferation of the reticulum cells had unmistakably assumed a morphologically tumorous character. In this context it is interesting to note that in the case of congenital myeloid leukemia published by Söderhjelm & Ranström the bone marrow was the site of focal reticulum cell proliferations of fundamentally the same type as in the cases reported here.

Thus, although most of the evidence suggests that in both cases it was a matter of a primary affection involving the reticuloendothelial-hemopoietic system, the question arises whether the observed tumorous proliferation constituted a final phase common to two separate disease entities affecting the hemopoietic apparatus or, alternatively, whether in the two cases the same fundamental disorder affected the reticuloendothelial system but was accompanied by dissimilar clinical manifestations from the hemopoietic apparatus, and hence gave rise to different peripheral blood pictures?

The first alternative would imply that

the two cases should be interpreted as one of congenital myeloid leukemia and one of congenital erythremia (di Guglielmo's disease), leading, in both cases, to terminal malignant reticulosis or reticulum cell sarcomatosis. In human beings such a development is well known among adults and it has been described in a newborn (cf. Söderhjelm & Ranström). As mentioned, no congenital case of erythremia seems to have been reported. Neither in di Guglielmo's disease nor in erythroblastemia, secondary to, for example, erythroblastosis or blood loss intra partum, has any description ever been published in the literature of the type of reticulum cell proliferation under discussion here.

The second alternative; that both cases represented the same basic disorder in the reticuloendothelial system though the clinical manifestations differed; would imply that one were dealing with Letterer-Siwe's non-lipoid reticulosis with myeloid (Case 1) and erythremic (Case 2) blood pictures. However, according to the literature, the leukocyte count is normal or depressed in Letterer-Siwe's disease. A few cases with high counts and atypical mononuclear cells in the peripheral blood have nevertheless been reported (7, 8), although an erythremic blood picture seems to be unknown in this disease. Together with the markedly pathological blood picture, the distribution within the organs of the tumoriform proliferations and the absence of tumour destructions in the skeletal tissues would seem to make this second alternative less likely than the first but does not rule it out altogether.

Accordingly the most plausible explanation would seem to be that in these two cases one must consider two separate

primary affections of a neoplastic type involving the hemopoietic system where, however, cell maturation had been inhibited to the extent that in Case 1 the majority and in Case 2 a portion of the cells had failed to develop beyond the reticulum cell (or hematoblast) stage. But this interpretation should not be accepted as final. It seems appropriate here to recall and emphasize Burgstedt & Hartl's statement that, in view of our inadequate knowledge about proliferative changes in the reticuloendothelial system, including the hemopoietic apparatus during the prenatal and neonatal period, it is yet too early to attempt to classify the various conditions. Hence it is important that additions to our collected knowledge regarding these problems are made in the form of publications describing such, on the whole, rare disorders before attempts are made to lay down principles for classification and differential diagnosis.

Summary

Two fatal cases of congenital blood disease are reported. Clinically both cases showed thrombopenia with a hemorrhagic diathesis, anemia, jaundice, and hepatomegaly; at autopsy an extensive proliferation of reticulum cell elements of definitely tumorous character was found, particularly in the bone marrow, lymph nodes, and skin; but also in other tissues. The two cases differed chiefly with respect to the blood picture, one of the cases presenting a highly immature myeloid leukemia, the other case showing an atypical erythropoiesis of erythremic character leaving the myelopoiesis essentially unaffected. Because of our inadequate know-

ledge of congenital blood diseases it is difficult to make a definitive diagnosis in these cases. The most plausible explanation seems to be, however, that they are two separate affections primarily involving different parts of the hemopoietic

system with different effects on the blood picture, but with similar end stages of severe inhibition of cell maturation with formation of a tumour tissue of the reticulum cell sarcoma type in the hemopoietic system, as well as in other tissues.

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The Iodine Content of Human Milk in Finland

by PIRKKO LAHESMAA and PANU VILKKI

Relatively few studies have been published on the iodine content of mother's milk. Thus Scheurlen (1926) in 12 samples found iodine contents varying from 15-150 $\mu\text{g/L}$. It has been found that during the first days of lactation the iodine content of mother's milk is very high, 240-260 $\mu\text{g/L}$, but declines rapidly over 5 days to about 50 $\mu\text{g/L}$ (Maurer & Diez; v. Fellenberg; Elmer & Rycklik). The milk of mothers in a goitrous area contains on the average less iodine (28 $\mu\text{g/L}$) than that of mothers in a non-goitrous area (43 $\mu\text{g/L}$) (Hercus & Roberts). Turner, however, reported results that were entirely the opposite: in the goitrous area an average of 145 $\mu\text{g/L}$ and in the non-goitrous area an average of 124 $\mu\text{g/L}$. He stated that the higher concentration of iodine in the milk of mothers in a goitrous region is believed to be due to compensatory activity on the part of the mother's thyroid gland. Individual values of 26 $\mu\text{g/L}$ (Maurer & Duerue) and 75 $\mu\text{g/L}$ (Eyekerman) have also been reported. Iodine values in human milk vary partly also due to the iodine content of the food and the secretory capacity of the epithelium of the mammary glands. Therefore they indicate only the normal values for their own

geographic area and are dependent in part upon the food iodine content. This reflects the same endemic geographic variation as does the urinary excretion of stable and radioactive iodine in Finland. (Wahlberg *et al.*; Lamberg *et al.*)

In studying the rôle of iodine deficiency in the etiology of endemic goitre in Finland, the question arises as to the iodine obtained by newborn and suckling infants in their diet. Since mother's milk is the principal diet at this age, attention is drawn chiefly to the iodine content of mother's milk.

Material and Method

The material consisted mostly of samples obtained from milk sent to the Mother's Milk Centre in the city of Turku. The samples were taken each month for one year. A total of 107 milk samples from 42 mothers was obtained during this period. The milk received by the Mother's Milk Centre at Turku came from an area with a low incidence of endemic goitre. For comparative material we received 18 milk samples from the Kuopio area, where the incidence of endemic goitre is higher than the mean incidence for Finland. The geographic location and goitre incidences of these two areas are shown in Fig. 1. From the Mother's Milk Centre at Kuopio we received 8 samples

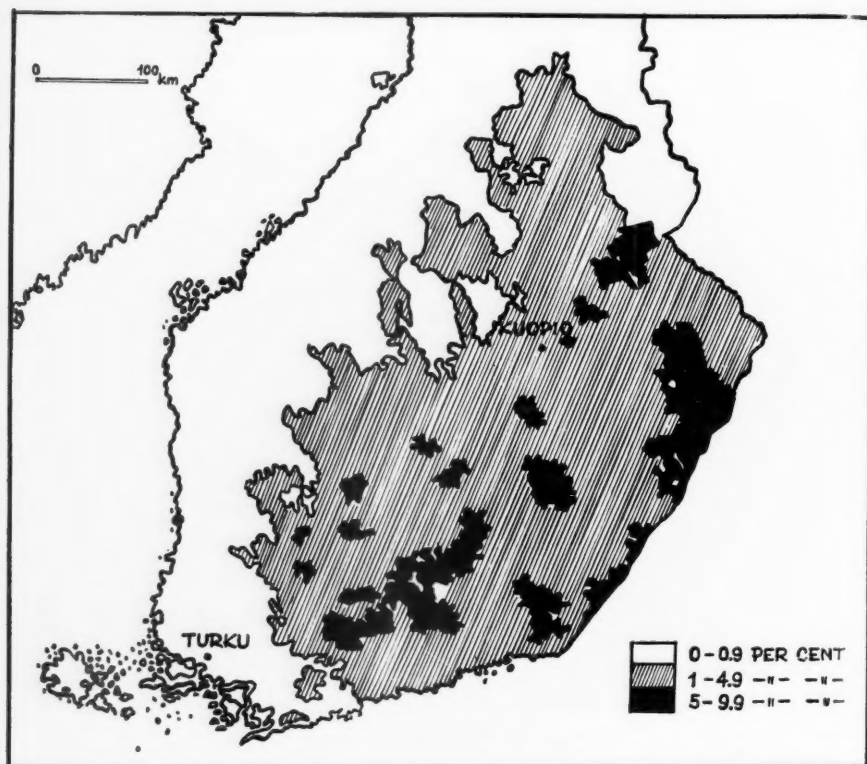


Fig. 1. Distribution of goitre in Finland (according to Wahlberg).

in August and 10 samples in December, totalling 18 samples from the same number of mothers.

To determine the iodine content at different times during the day, we obtained samples from 5 mothers in Turku. These samples were taken in connection with each feeding for a period of 24 hours.

In 10 mothers in Turku we determined, simultaneously, the iodine content in the milk and the serum protein bound iodine.

In response to our inquiry it was learned that hypo- or hyperthyreosis had not been diagnosed in any of the milk donors. The use of iodised salt was equally common in Turku and in Kuopio (about 90 per cent in this material).

The method of iodine determination used has been described earlier (Vilkkii).

Results

1. The individual and mean iodine contents.

The mean iodine content of mother's milk in the Turku area was $53.3 \pm 1.4 \mu\text{g/L}$ (107 samples) and in the Kuopio area $25.1 \pm 1.6 \mu\text{g/L}$ (18 samples). The difference is highly significant. The distribution of the individual results is shown in Fig. 2.

2. The seasonal variation

The mean iodine content for each month of the samples from the Mother's Milk

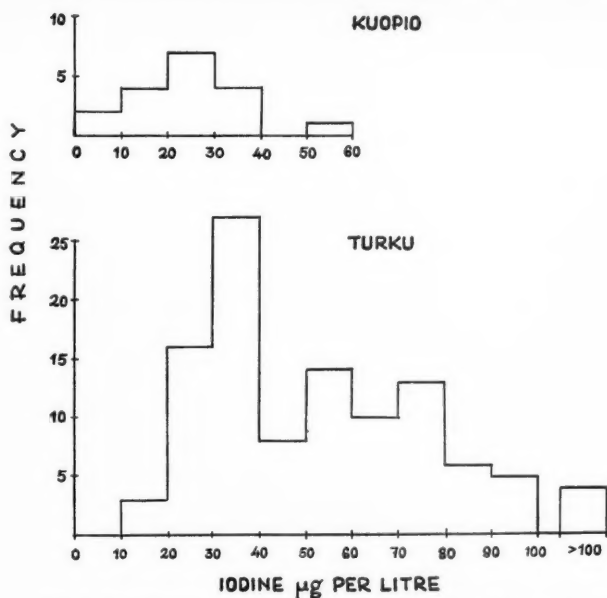


Fig. 2. Distribution of milk samples according to their iodine content.

TABLE 1. *Seasonal variation in iodine contents of samples from Mother's Milk Centre of Turku.*

Month	Number of samples	Mean iodine content $\mu\text{g/L}$	S.D. of mean
January	5	48.0	6.8
February	5	40.4	4.1
March	5	77.0	12.2
April	9	54.6	10.0
May	12	65.1	7.6
June	13	44.4	5.2
July	7	37.0	5.1
August	8	32.5	5.5
September	7	55.9	8.0
October	10	47.0	6.4
November	12	68.4	10.1
December	14	59.1	5.8
Whole year	107	53.3	1.4

Centre of Turku is seen in Table 1 and Fig. 3. The mean iodine content of the samples from Kuopio was slightly lower in

August ($23.3 \pm 3.2 \mu\text{g/L}$) than in December ($26.5 \pm 4.6 \mu\text{g/L}$) but the difference is not statistically significant. The mean values for Turku for these two months show a significant difference between the iodine content of human milk in August ($32.5 \pm 5.5 \mu\text{g/L}$) and in December ($59.1 \pm 5.8 \mu\text{g/L}$) (Fig. 4).

3. The diurnal variation

The variation over a period of 24 hours in the milk iodine content of 5 mothers is shown in Fig. 5. The differences between the highest and the lowest content for each individual varied from 19–42 $\mu\text{g/L}$. A common feature in these 5 mothers was the occurrence of the highest iodine concentrations of milk during the night although at differing times.

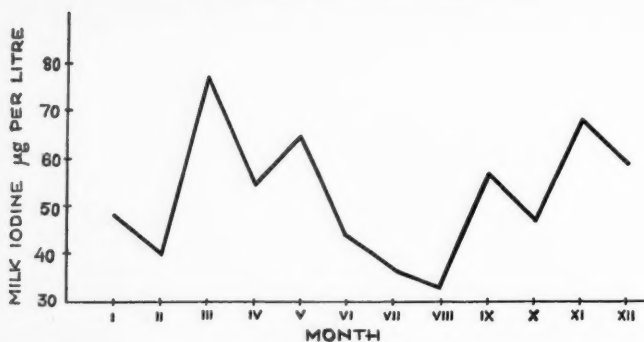


Fig. 3. Monthly variations in iodine content of mother's milk in the Turku area.

4. The simultaneous variation with the serum protein bound iodine

Milk iodine and serum protein bound iodine were determined simultaneously in 10 mothers (Table 2). No correlation was found between these two values ($r = 0.53$).

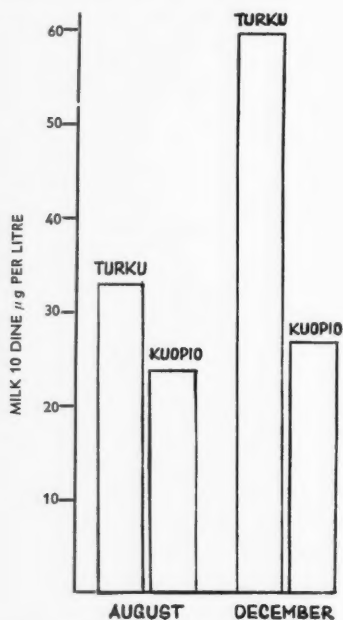


Fig. 4. — Mean iodine content of mother's milk for two months of the year in the non-goitrous Turku area and the goitrous Kuopio area.

Discussion

A comparison of the mean iodine content of mother's milk in the Turku and Kuopio areas and the iodine content of cow's milk determined by Vilkki, which were 45 µg/L in the Turku area and 28 µg/L in the Kuopio area, shows that the values have the same trend, even if the difference appears to be still greater in the case of human milk. Our results are compatible also with those of Hercus & Roberts in the finding that the iodine values of human milk in a goitrous area are lower than those in a non-goitrous area. Thus the contrary results obtained by Turner are not supported by the present investigation.

According to Vilkki, the mean iodine content of cow's milk is lower during the pasturage season than during the barn feeding season. During the latter the animals usually are given a larger amount of mineral feed. Milk and dairy products form our most important source of dietary iodine (Vilkki). It seems natural that the iodine content of mother's milk is lowest during the summer, as is shown by our results.

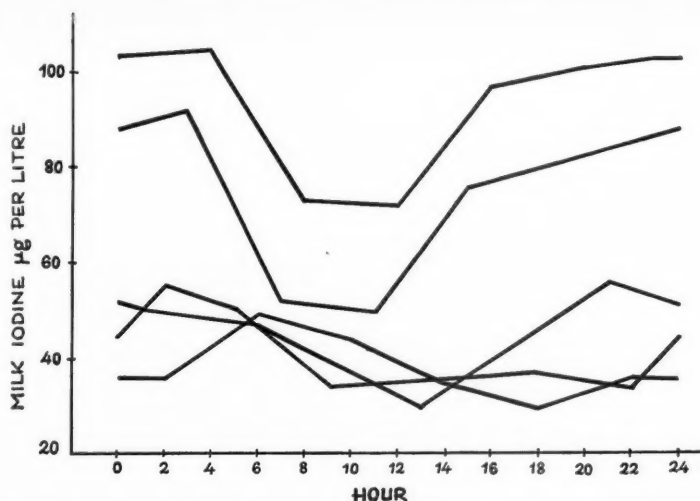


Fig. 5. Variations in the iodine content of the milk of 5 mothers over a period of 24 hours.

The observed daily rhythm in the iodine content is neither convincing nor specific for iodine.

There exist no criteria for the determination of the iodine requirement of newborn and suckling infants. Salter considered the minimum iodine requirement of children in general to be 50 µg/24 h.

TABLE 2. *Simultaneous determinations of the iodine in the milk and of the protein bound iodine in the serum of 10 mothers in the Turku area.*

	Milk iodine content µg/L	Serum P.B.I. µg/100 ml
1.	101	6.0
2.	36	8.1
3.	58	7.7
4.	30	6.7
5.	92	8.6
6.	36	11.1
7.	36	6.8
8.	52	6.1
9.	36	7.9
10.	49	4.4

According to this value, the iodine intake from mother's milk by sucklings would not be adequate even in the Turku area. The difference observed by us in the iodine content of human milk in a goitrous and a non-goitrous area gives reason to presume that iodine deficiency may occur even in infancy in the endemic goitrous area of Kuopio. This may be a significant preliminary initial supporting factor in the development of endemic goitre.

Summary

The iodine content was determined in samples of mother's milk obtained from two areas of Finland which differ in the incidence of goitre. The mean iodine content of mother's milk was found to be 53.3 ± 1.4 µg/L in 107 milk samples from 42 mothers in the non-goitrous Turku area and 25.1 ± 1.6 µg/L in 18 milk samples from 18 mothers in the goitrous Kuopio area. The difference between the two

mean values is highly significant. The mean iodine content of samples taken in August was lower than that of samples taken in December, but this difference was statistically significant in the Turku area only. No convincing daily rhythm

was observed in the iodine content of human milk, and no correlation was found between the iodine content of the milk and the level of the protein bound iodine in the serum of the mother.

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Indications for Exchange Transfusion in Newborn Infants with Hyperbilirubinaemia not due to Rh Immunization¹

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The toxic effect of hyperbilirubinaemia on the nerve cells of the basal ganglia of newborn infants is established (7, 11, 14, 21, 28). By treating patients suffering from erythroblastosis foetalis with one or several exchange transfusions it has become possible to keep the serum bilirubin concentration below 20 mg/100 ml, and to prevent almost completely the appearance of kernicterus (1, 22, 26). It is generally agreed that the critical serum bilirubin level is about 20 mg/100 ml in cases of erythroblastosis foetalis. This is not an absolutely critical level, however, but below it the risk of kernicterus is very low.

Hyperbilirubinaemia and kernicterus are seen also in otherwise healthy neonates, especially premature infants, but it is not at all certain that the critical level of 20 mg/100 ml is valid also for these neonates. Dine (9) stated that kernicterus can be expected when the serum bilirubin exceeds 16 mg/100 ml in premature infants. Crosse, Meyer, & Gerrard (5) estimated the risk of kernicterus to be 66 % in premature infants with bilirubin values over 18 mg/100 ml. MacLean, Lucey, & Harris (18) found kernicterus in three premature infants, in whom the serum bilirubin con-

centration never exceeded 12.6, 13.2, and 15.2 mg/100 ml respectively. In a group of 18 premature infants having a maximum serum bilirubin concentration of 20-25 mg/100 ml Vest (27) noted two cases of kernicterus, and in 11 premature infants with a maximum serum bilirubin of over 25 mg/100 ml he found five cases. Crosse, Wallis, & Walsh (6) estimated the incidence of prematurity kernicterus to be 1.08 % of all admissions. Others have given lower figures for the risk (13, 20).

In full-term newborn infants the incidence of hyperbilirubinaemia and kernicterus is much lower. Though high serum bilirubin levels are occasionally seen, figures above 12 mg/100 ml are said to be exceptional (2, 13, 24, 29). In a selected group of 24 full-term infants with serum bilirubin levels of over 12 mg/100 ml, Brown & Zuelzer (3) found values exceeding 18 mg/100 ml in 16 cases and exceeding 20 mg/100 ml in 9 cases. Claireaux, Cole & Lathe (4) denied the existence of kernicterus in full-term infants except in connection with erythroblastosis foetalis. Zuelzer & Mudgett (30), however, reported 32 cases of kernicterus not associated with Rh immunization, and 9 of them were full-term. During 1950-1955 we saw in our Clinic 18 full-term newborn infants with profound jaundice of the "physio-

¹ This investigation was supported by grants from the Swedish Medical Research Council.

logical" type. Three of these 18 infants developed kernicterus. Thus there does seem to be some risk of kernicterus in full-term newborn infants not suffering from erythroblastosis foetalis.

The method of choice in treating hyperbilirubinaemia and preventing kernicterus is exchange transfusion (*cf.* 16), and several authors have strongly advocated and performed exchange transfusion also in neonates with hyperbilirubinaemia not due to known red-cell sensitization (3, 5, 6, 12, 17, 23). The indications for exchange transfusion are not established, however, and the practice in different centres differs widely. Crosse, Wallis & Walsh (6) have chosen a serum bilirubin of 18 mg per 100 ml as a criterion for exchange transfusion in premature infants. Brown & Zuelzer (3) performed exchange transfusions in premature and full-term neonates in whom the serum bilirubin exceeded 20 mg/100 ml. Dundon (10) regarded 30 mg/100 ml as a critical level. Newns & Norton (23) recommend transfusion in all infants whose serum bilirubin concentration reaches 30 mg/100 ml, and also in infants with a serum bilirubin below 30 mg/100 ml, if they become lethargic, irritable, or difficult to feed, or if there is a rapid rise in the serum bilirubin on the 3rd or 4th day. In many centres exchange transfusions are never performed in infants with hyperbilirubinaemia of the "physiological" type.

The seriousness of kernicterus makes it important to determine as exactly as possible, when exchange transfusion should be performed in newborn infants with hyperbilirubinaemia. As the exchange procedure itself is not without risk, this becomes still more important.

The purpose of the present investigation was to study the incidence of jaundice and hyperbilirubinaemia not due to Rh immunization in an unselected group of newborn infants, to assess the risk to infants showing high serum bilirubin concentrations and to establish when and in which of these infants treatment with exchange transfusion is indicated.

Plan of Investigation

It is always difficult to establish in retrospect a possible association between neurological disorders and neonatal hyperbilirubinaemia. In order to be able to clarify such a relationship it seems more satisfactory to study a group of infants from birth over a period of several years with special regard to initial hyperbilirubinaemia, intellectual and physical development, and the possible occurrence of neurological abnormalities. Such an investigation may be performed in two different ways. Either a whole group of untreated infants with hyperbilirubinaemia may be followed up or this group may be divided into two sub-groups of treated and untreated infants. The second alternative is preferable, because it permits a comparison between two groups handled similarly in every respect except with regard to the special treatment for the hyperbilirubinaemia.

In the present investigation it was decided to study the full-term infants according to this principle, and to compare in detail a group of infants treated with exchange transfusion with a group of untreated infants. In premature infants with hyperbilirubinaemia the incidence of kernicterus is high. Previous experience

has shown that exchange transfusion is an effective and safe method of treatment in some of these cases, and it was therefore considered impossible on ethical grounds not to perform exchange transfusion in half of these infants.

Material

The series consisted of all infants born at the University Hospital in Uppsala during 1957 and 1958 (about 2300 yearly), with the exception of those suffering from erythroblastosis foetalis, septicaemia, or obstructive jaundice. It may be added that, with a few exceptions, all births in the district take place at the Hospital. The newborn infants were carefully supervised, especially with regard to jaundice. In those showing marked jaundice the serum bilirubin concentration was determined daily until steadily falling values were obtained.

Exchange transfusion was performed alternately in 95 *full-term new-born infants* (68 boys and 27 girls) with a serum bilirubin concentration reaching 20 mg/100 ml, and those not exchanged were used as controls. In all, 46 infants¹ were treated, and the number of controls was 48. In three cases the exchange transfusion was repeated once, and in a fourth case twice. Among the full-term infants 21 were considered to have haemolytic disease due to A or B immunization, the diagnosis being based on the finding of "immune" anti-A or anti-B antibodies in the mother's serum. In 15 of these cases an exchange transfusion was performed and 6 were not so treated. These infants with haemolytic disease present a special problem. Because of the difficulties of establishing the diagnosis with confidence at the time when the serum bilirubin reached 20 mg/100 ml, it was decided from the start of the investigation to include them in the

¹ According to the principles of the investigation the serum bilirubin-concentration should be kept below 20 mg/100 ml. By mistake 1 infant in whom the level rose to 23.6 mg/100 ml after the first transfusion was not subjected to repeat exchange transfusion. This case was therefore not included in the series.

series and to treat them according to the general principles outlined. Some of them, however, differed markedly from the other full-term infants in the series, and thus it became necessary to present the cases of ABO haemolytic disease separately. The final main series of full-term newborn infants will thus include only those with hyperbilirubinaemia not due to haemolytic disease, and consists of 42 untreated and 31 treated infants.

Exchange transfusion was performed in 23 *premature infants* (7 boys and 16 girls), 15 of them treated when the serum bilirubin level reached 20 mg/100 ml, and 8 when the level was between 15 and 20 mg/100 ml because they showed neurological signs. In 3 cases the exchange transfusion was repeated once, and in a fourth case it was repeated twice. Of the premature infants 1 weighed less than 1500 g at birth, 10 between 1500 and 2000 g, and 12 between 2000 and 2500 g. No cases of ABO haemolytic disease were recorded among the premature infants. As controls to the treated group we have used the untreated premature infants born in Uppsala during 1954 and 1955. The infants born in 1956 could not be used because preliminary studies, necessary for the planning of the present investigation, were started that year. The treated group of premature infants and their controls could be compared only with respect to mortality rate and incidence of kernicterus, mainly because the principles for determining serum bilirubin differed in the two groups. The premature infants born in 1957 and 1958 were regularly given 2 mg of vitamin K (Menadiol Sodium Diphosphate) intramuscularly. During 1954 and 1955 a higher dose of vitamin K was given, but the total amount never exceeded 10 mg in each infant. No sulphonamide preparations were given to the premature infants.

All infants in both groups were carefully observed, especially with regard to neurological signs and to the immediate effect of exchange transfusion.

A follow-up study was also outlined. All infants were examined at the ages of 5-8 weeks and 3-4 months with regard to neu-

rological signs and development. A third follow-up examination is planned to take place when the infants have reached the age of 2 years.

Methods

The blood samples were taken by a deep heel prick. During the exchange transfusion blood samples were taken from the umbilical vein via the catheter.

The haemoglobin concentration of whole blood was measured as oxyhaemoglobin with a photoelectric haemoglobinometer, Haemotest (Testa-laboratorium, Vedbaek, Denmark).

The reticulocyte count was determined after staining with brilliant cresyl blue, as described by Seip (25).

During 1957 the serum bilirubin concentration was determined by the method of Jendrassik & Grof (14 a), and in 1958 by that of Malloy & Evelyn (19), modified for 0.2 ml of serum. A comparison of the two methods, based on 35 duplicate determinations, showed a good correlation for serum bilirubin values below 20 mg/100 ml. At higher concentrations the method of Malloy & Evelyn gave slightly higher values. The 1958 assays included determinations of directly reacting bilirubin. In the following all bilirubin values are given as total bilirubin. The concentration of directly reacting bilirubin was very low in all cases, and never exceeded 2.8 mg/100 ml.

The exchange transfusions were as a rule performed through the umbilical vein. In 2 cases it was necessary to use the saphenous vein, and in 2 others the femoral vein. During 1957 whole acid-citrate-dextrose blood (100 ml ACD to 400 ml blood) was used. During 1958 we used sedimented acid-citrate-dextrose blood from which about 150 ml of the supernatant had been removed. The donor blood was never more than 72 hours old. In all, 170 ml of blood was given per kg of body-weight, each portion being 10–15 ml in the premature infants and 20 ml in the full-term infants. In order to avoid overloading of the circulation, a blood deficit of 10–20 ml was maintained in the infant throughout the exchange procedure, and the

venous pressure was repeatedly measured. The venous pressure was normal in all instances. The blood given was compatible with the infant's with regard to the ABO blood group and to the D (Rh_0) factor of the Rh system, except in those cases where the mother belonged to Group O and the infant to Group A or B, in which cases O blood was used. The duration of the exchange transfusions varied between 50 and 90 minutes, and the procedure usually took about 60 minutes. During 1957, when whole acid-citrate-dextrose blood was given, 1 ml of 10% calcium gluconate was administered for each 100 ml of blood given. During 1958 no calcium gluconate was given. Terramycin was given to all infants in whom an exchange transfusion was performed. No untoward reactions were noted during or after the exchange transfusions. In 1 infant, however, in whom the exchange transfusion was performed via the right femoral vein, swelling of the right leg was noticed for one week after the transfusion.

The serological investigations were performed by standard methods. All mothers and infants were investigated with regard to the ABO blood group and the D (Rh_0) factor of the Rh system. In the case of ABO incompatibility samples of blood from mother and infant were sent to the Blood Grouping Laboratory in Stockholm for investigation of "immune" anti-A or anti-B. Coombs's direct test was performed on the red cells of all infants.

Results

Incidence of jaundice and hyperbilirubinaemia

The incidence of icterus and hyperbilirubinaemia was calculated in those infants who survived the first 48 hours.

During 1957 29.5% of the full-term newborn infants and 72% of the premature infants were icteric. For 1958 the incidence of jaundice was calculated only for the premature infants, and a figure of 6% was obtained. Some of the icteric infants

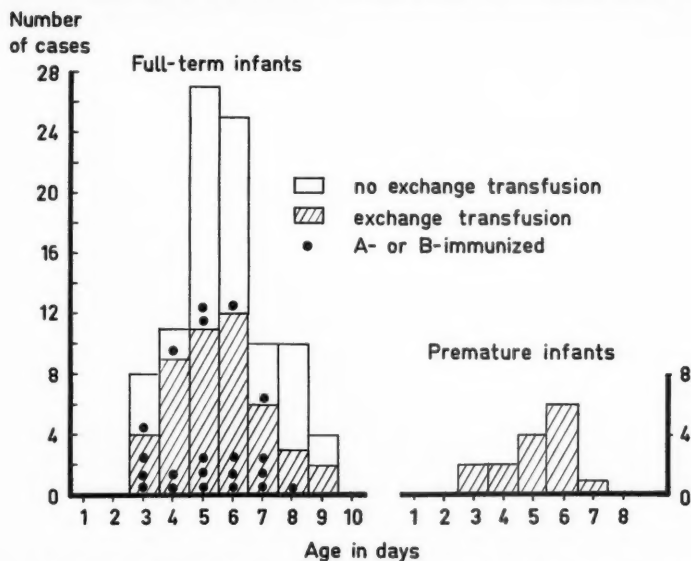


Fig. 1. Day of life at which the serum bilirubin rose to 20 mg/100 ml in 95 full-term and 15 premature newborn infants.

reached high serum bilirubin levels. Of the full-term infants 2.7 % showed a bilirubin value above 20 mg/100 ml in 1957, and in 1958 the corresponding figure was 1.9 %. In 1957, 10 % of the premature infants showed a serum bilirubin concentration exceeding 20 mg/100 ml, and in 1958 the figure was 9 %.

In Fig. 1 the full-term infants are arranged according to the day of life when the serum bilirubin level reached 20 mg/100 ml. It is seen that this value was never reached before the 3rd day, and never after the 9th day. Most of the infants showed a bilirubin value exceeding 20 mg/100 ml for the first time on the 5th or 6th day of life. In the infants with ABO haemolytic disease the hyperbilirubinaemia seems to appear slightly earlier than in the others.

In Fig. 1 the premature infants are also arranged according to the day of life when

the serum bilirubin level reached 20 mg/100 ml. As can be seen, this level was reached at about the same time as in the full-term infants.

Full-term infants with hyperbilirubinaemia not due to ABO haemolytic disease

Condition and findings before serum bilirubin reached 20 mg/100 ml. The 42 untreated and the 31 treated infants were in all pertinent respects quite comparable until the exchange transfusion was performed. Slight lethargy was observed in 10 of the untreated and in 10 of the treated infants. In the untreated group 1 of the lethargic infants showed a pathological Moro reflex. In the treated group there were 2 infants with an abnormal Moro reflex, 1 of whom had probably had intracranial bleeding. There were no other neurological signs. The haemoglobin concentration and the reticulocyte count did

Serum bilirubin,
mg/100 ml

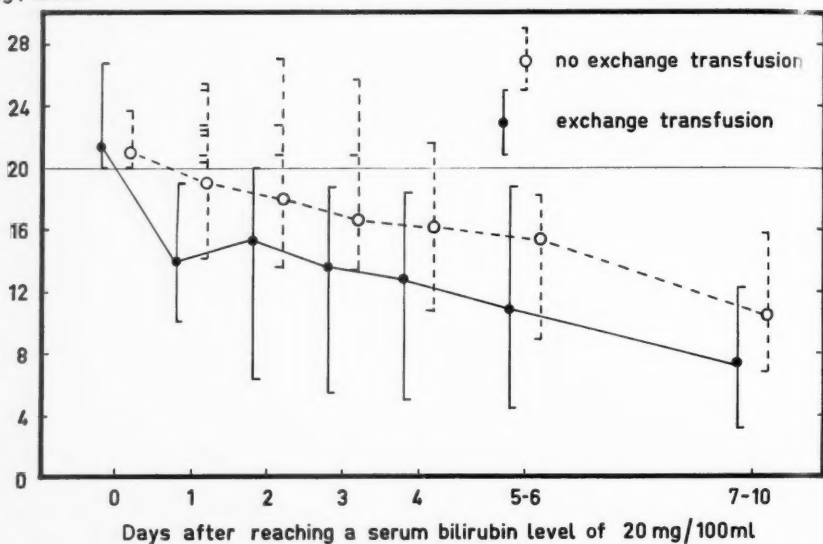


Fig. 2. Serum bilirubin concentration in 24 untreated and 19 treated newborn infants (1957) during the 7-10 days following the day when the serum bilirubin reached 20 mg/100 ml. The average values of the untreated infants are marked \circ , and those of the treated infants \bullet . The horizontal bars indicate individual cases (range, and values above 20 mg/100 ml).

not deviate in the two groups, and all values fell within the normal ranges.

Condition and findings immediately after the serum bilirubin reached 20 mg/100 ml. As to general condition, lethargy, and neurological signs, there was no difference between the two groups. Of those infants who were not treated by exchange transfusion, but who were slightly lethargic, 6 improved rapidly after the bilirubin had reached 20 mg/100 ml, 3 remained lethargic for several days, and 1 became more lethargic. In the one infant in whom a pathological Moro reflex was observed, the reflex did not become normal until six days later. Of infants treated by exchange transfusion and lethargic before treatment, 7 improved immediately after

treatment, 2 remained uninfluenced, and 1 became more lethargic. One of the 2 infants with an abnormal Moro reflex improved immediately after the exchange transfusion, while the other one (with the probable intracranial bleeding) remained lethargic and showed an abnormal Moro reflex for several days. Two infants who showed no abnormal signs on the day of exchange transfusion, became slightly lethargic on the next day and remained so for some days.

In the group of untreated infants a spontaneous and rapid fall in serum bilirubin concentration took place in most cases (Figs. 2 and 3), commencing shortly after the serum bilirubin had reached 20 mg/100 ml. In 18 of these untreated

Serum bilirubin,
mg/100 ml

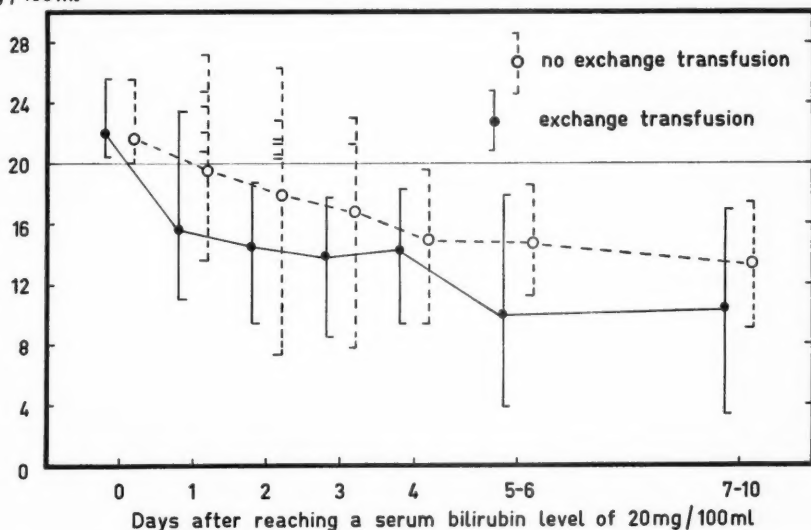


Fig. 3. Serum bilirubin concentrations in 18 untreated and 12 treated newborn infants (1958) during the 7-10 days following the day when the serum bilirubin reached 20 mg/100 ml. The average values of the untreated infants are marked \circ , and those of the treated infants \bullet . The horizontal bars indicate individual cases (range, and values above 20 mg/100 ml).

infants, however, the serum bilirubin remained at between 22.0 and 27.2 mg/100 ml for one or several days. Those 5 infants who showed the highest values had a maximum bilirubin concentration of 27.2, 27.2, 25.0, 24.7, and 23.8 mg/100 ml. A bilirubin concentration exceeding 20 mg/100 ml was found in 7 infants for a period of 4-5 days. It was not until after the 5th day that all infants in the untreated group showed serum bilirubin values below 20 mg/100 ml. In the group of treated infants a very marked fall in the serum bilirubin took place in all cases during the exchange transfusion. During the next 24-28 hours, the serum bilirubin level again began to rise. In only 1 case did it come to exceed 20 mg/100 ml, and in this case a second exchange transfusion

was performed. The difference in bilirubin levels between the untreated and the treated infants during the period following the day when the serum bilirubin levels reached 20 mg/100 ml is seen in Figs. 2 and 3.

The effect of the exchange transfusion on haemoglobin concentrations and reticulocyte counts will be presented in a separate paper (Killander, Müller-Eberhard, & Sjölin).

Full-term infants with hyperbilirubinaemia due to ABO haemolytic disease

Condition and findings before the serum bilirubin reached 20 mg/100 ml. By adhering to the principle of selecting cases for exchange transfusion, 6 were untreated and 15 treated. In most of the 21 infants

with ABO haemolytic disease the general condition was good. Slight to moderate lethargy was observed in 5 infants, 2 of them belonging to the untreated group and 3 to the treated group. In the untreated group both of the lethargic infants showed a pathological Moro reflex, but no other neurological signs were observed. In the untreated group 3 infants showed definite signs of a haemolytic process with increased reticulocyte counts (18.0, 8.7, and 8.7%, respectively) but no anaemia. In the treated group 3 infants had an elevated reticulocyte count (15.4, 10.3, and 8.4% respectively). These 3 infants also had a moderately low haemoglobin concentration (14.7, 14.9, and 16.7 g/100 ml respectively). Otherwise the haemoglobin values and the reticulocyte counts were normal. The direct Coombs's test was positive in 1 of the treated infants.

Condition and findings after the serum bilirubin reached 20 mg/100 ml. Concerning the general condition, lethargy, and neurological signs, there was no clear difference between the untreated and the treated groups. The 2 untreated infants who were lethargic when the serum bilirubin passed 20 mg/100 ml remained so, and had an abnormal Moro reflex during the next six and nine days. Two of the treated infants who were lethargic before treatment improved immediately afterwards, and the third one remained uninfluenced by the exchange transfusion.

In all of the untreated infants a spontaneous and rapid fall in serum bilirubin concentration was observed after the 20 mg/100 ml level had been reached. This also happened in those 3, who had a raised reticulocyte count. In the treated group all infants showed a rising serum

bilirubin concentration during the first 24 hours after treatment. In only 5 cases, however, did it again increase to values above 20 mg/100 ml. Two of these are of special interest because they had shown clinical signs of an active haemolytic process before treatment, viz., slightly reduced haemoglobin values and raised reticulocyte counts. The highest bilirubin values recorded in these infants were 31.5 and 26.4 mg/100 ml. In 1 case the exchange transfusion was repeated twice and in the other it was repeated once. In another infant with a second bilirubin peak of over 20 mg/100 ml the haemoglobin concentration and the reticulocyte count were normal, but the direct Coombs's test was positive. In this case too, a second exchange transfusion was carried out. The other 2 infants who showed a second bilirubin peak of over 20 mg/100 ml were not subjected to a second exchange transfusion because the serum bilirubin concentration started to fall immediately, and continued to decline rapidly.

During the week after the day when the serum bilirubin had for the first time reached 20 mg/100 ml, slight anaemia was noticed in two of the infants treated by exchange transfusion (Hb 13.9 and 14.7 g/100 ml). One was treated in 1957, the other in 1958. All other infants of this group showed normal haemoglobin values during the period immediately following the exchange transfusion.

Premature infants with hyperbilirubinaemia

Condition and findings before exchange transfusion. Of those 15 premature infants, in whom the serum bilirubin reached 20 mg/100 ml (in 3 it exceeded 22 mg/100 ml but not 23.8), 5 were lethargic and diffi-

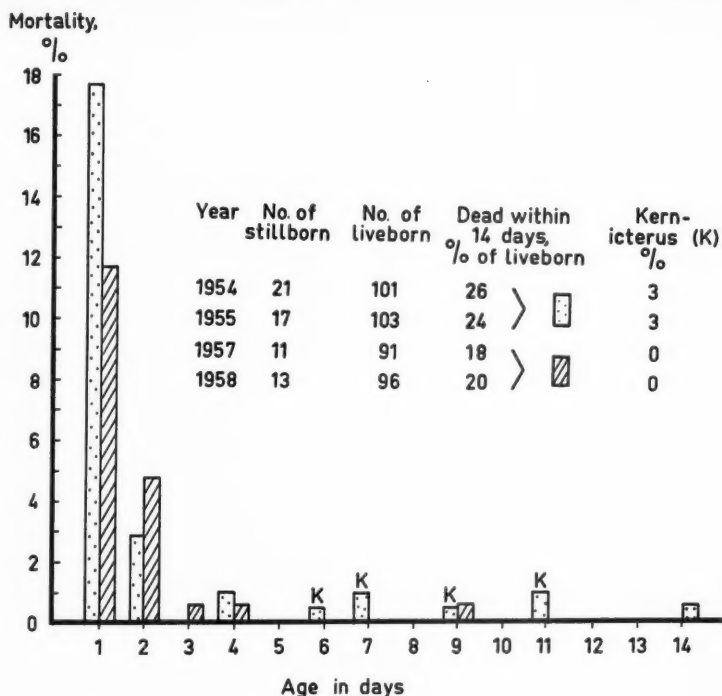


Fig. 4. Mortality during the first 14 days of life for the premature infants born in 1954-55 and 1957-58.

cult to feed. Those 8 infants who were treated by exchange transfusion at a bilirubin level of 15-20 mg/100 ml were all lethargic, and some of them very much so. Five of them had repeated attacks of cyanosis, in 2 the Moro reflex was negative, and 3 had typical sclerema. The haemoglobin values and the reticulocyte counts were in all cases within the normal ranges for premature infants of this age.

Condition and findings after exchange transfusion. Immediate and striking improvement was observed in 7 infants, and 3 were slightly improved. In 3 infants, weighing 1360, 1770, and 1910 g respec-

tively at birth, the general condition and the lethargy were quite uninfluenced by the exchange transfusion.

During the 24 hours following the exchange transfusion an increase in serum bilirubin was regularly observed. The serum bilirubin rose to values above 20 mg/100 ml in 4 cases (24.6, 22.1, 21.0 and 20.2 mg/100 ml). In 3 of these cases exchange transfusion was repeated once, and in 1 it had to be repeated twice.

A low haemoglobin was observed one week after exchange transfusion in 6 infants born in 1957 but in none born in 1958 (cf. 15). A rapid fall in reticulocyte

count was seen immediately after exchange transfusion in all cases, irrespective of the type of blood given.

In Fig. 4 the treated group of premature infants born during 1957 and 1958 is compared with the untreated premature infants born 1954 and 1955 with regard to mortality within the first 14 days of life and with regard to the incidence of histologically proved kernicterus. The mortality was about 25 % in 1954-55 and about 19 % in 1957-58. The significance and cause of this difference are difficult to assess. Of the live-born premature infants with hyperbilirubinaemia not treated with exchange transfusions, 3 % died from kernicterus. During 1957-58, when exchange transfusions were carried out routinely, none died from kernicterus.

First and second follow-up examinations
(5-8 weeks and 3-4 months)

In the group of full-term infants, including the babies born to ABO immunized mothers, most of the 48 controls were seen by us, and none of them was found to show either neurological signs or signs of retarded development. Two of the infants we were unable to see ourselves, but information was obtained from the Child Welfare Clinic that there were no abnormal neurological signs or mental retardation.

None of the 46 infants treated with exchange transfusion was found to have neurological or developmental abnormalities. This group includes the infant with suspected intracranial haemorrhage and 1 infant with hypothyroidism in whom treatment with desiccated thyroid was started when she was nine weeks old.

Nor among the 23 premature infants was there any with definite neurological or developmental abnormalities at 5-8 weeks or 3-4 months. In 1 infant in this group a diagnosis of hydrocephalus internus was made when he was 4½ months old, and he showed retarded physical and mental development later on.

Comments

It is well known that hyperbilirubinaemia (> 20 mg/100 ml) not due to Rh immunization is a common finding in premature infants. The incidence of hyperbilirubinaemia in this investigation was about 10 %, which is in accordance with the findings reported by other workers. In full-term newborn infants the incidence of hyperbilirubinaemia of this type is lower, and in this investigation was about 2.3 %. No figures for the incidence of hyperbilirubinaemia in an unselected group of full-term infants have, to our knowledge, been published previously.

From the results of the present investigation, it is for the time being not possible to state definitely the indications for exchange transfusion in newborn infants with hyperbilirubinaemia not due to Rh immunization. In spite of the short period of observation, however, some preliminary suggestions may be made.

Concerning full-term infants with no signs of haemolytic disease, there were no differences between untreated infants and those treated by exchange transfusion. All were healthy at the age of 3-4 months, and no case of kernicterus was diagnosed. Moreover, 18 infants in the untreated group showed bilirubin levels between 22.0 and 27.2 mg/100 ml for one or several

days, and never showed signs of brain damage.

It is difficult to make a comparison between the untreated and the treated infants with A or B haemolytic disease, because the majority of these infants (15 out of 21) were treated by exchange transfusion and because those showing the most persistent tendency to hyperbilirubinaemia all belonged to the treated group. There was no difference between the 2 groups with regard to neurological abnormalities during the neonatal period and at the follow-up examinations. Up to the age of 3-4 months they did not differ from the other full-term infants.

The possible risk of kernicterus in full-term infants in whom the serum bilirubin is 20 mg/100 ml or more can be approximately calculated from the total number of infants investigated (94) and from the incidence of kernicterus (0) found. The incidence of kernicterus in such a group cannot be higher than 5% at a confidence level of 99%.

Consequently, exchange transfusions seem to be unnecessary at a bilirubin level of 20 mg/100 ml in full-term infants with hyperbilirubinaemia not due to haemolytic disease, and also in most infants with ABO haemolytic disease.

A special problem is encountered in those infants with ABO haemolytic disease who present definitely elevated reticulocyte counts (> 8%) with or without anaemia. In some of them the bilirubin concentration increases rapidly, and high levels are attained. These cases must be watched carefully and the bilirubin concentration determined once or twice daily during the first days of life. Exchange transfusion should be performed according

to the principles adopted for the treatment of erythroblastosis foetalis.

Of the 23 premature infants with hyperbilirubinaemia 10 showed neurological signs. In 7 of these cases marked improvement was noted immediately after the exchange transfusion. No case of kernicterus occurred among these 23 premature infants, whereas 6 died from kernicterus in 1954-55. These results indicate that exchange transfusion offers a reliable means of preventing kernicterus in premature infants.

All bilirubin determinations are subject to considerable systematic and accidental deviations with different methods and in different laboratories. Bilirubin values must therefore always be viewed critically, and their significance interpreted in connection with the clinical picture. Signs such as lethargy, irritability, feeding difficulties, attacks of cyanosis, and an abnormal Moro reflex arising during the first days of life may be early indications of impending brain damage. The decision to perform exchange transfusion must be based both on the degree of bilirubinaemia and on the appearance of early neurological signs. As full-term and premature infants seem to differ in their response to hyperbilirubinaemia, the indications for treatment cannot be uniform.

The result of this investigation indicates that exchange transfusion should be performed in all premature infants with early neurological signs and a bilirubin concentration above 15-20 mg/100 ml. The question of whether exchange transfusion should be performed in premature infants with hyperbilirubinaemia, but without any neurological signs remains open.

In full-term infants it is at present im-

possible to fix a critical bilirubin level at which exchange transfusion ought to be performed. It seems, however, reasonable to restrict exchange transfusion to those few infants who show excessive hyperbilirubinaemia (> 25 mg/100 ml), especially if combined with early neurological signs.

Summary

In order to clarify the indications for exchange transfusion in newborn infants with hyperbilirubinaemia not due to Rh immunization all infants born in Uppsala during 1957 and 1958 were observed with respect to the occurrence of hyperbilirubinaemia and neurological symptoms. In a consecutive series of 95 full-term infants, exchange transfusion was per-

formed in every second infant when the serum bilirubin reached 20 mg/100 ml. At the age of 3-4 months no difference was found between the treated and the untreated infants. None showed neurological abnormalities which could be related to the hyperbilirubinaemia. Exchange transfusions were also performed in 23 premature infants in whom the serum bilirubin level rose above 15-20 mg/100 ml. None of them showed signs of neurological abnormalities at 3-4 months, in contrast to the findings in 1954-55, when 6 premature infants died from kernicterus.

Acknowledgements

We wish to thank Miss Milly Börlin, Miss Aina Hellberg, Miss Lisbeth Pettersson, and Miss Gun Pettersson for skilful technical assistance.

Indications pour transfusions d'échange chez le nouveau-né atteint d'hyperbilirubinémie non causée par immunisation Rh

Afin de préciser les indications de transfusions d'échange chez les nouveaux-nés atteints d'hyperbilirubinémie non causée par immunisation Rh, tous les enfants nés à Upsal pendant les années 1957 et 1958 furent mis en observation pour la détection d'une hyperbilirubinémie possible et des symptômes neurologiques. Parmi une série de 95 enfants nés à terme, la transfusion d'échange fut faite sur un enfant sur deux quand la bilirubine atteignait 20 mg/100 ml. A l'âge de trois à quatre mois il n'existait aucune différence entre les enfants traités et non-traités. Aucun ne manifestait d'anomalies neurologiques qui eussent pu étre imputées à l'hyperbilirubinémie. Des transfusions d'échange furent faites également sur 23 prématurés chez lesquels la bilirubine dépassait 15-20 mg/100 ml. Aucun d'entre eux ne manifesta d'anomalie neurologique à l'âge de trois ou quatre mois, à l'encontre des observations faites en 1954-1955 où six prématurés étaient morts d'un ictere nucléaire.

Indikationen für eine Austauschtransfusion bei Neugeborenen mit nicht auf Rh-Immunisierung beruhender Hyperbilirubinämie

Um zu klären, wann eine Austauschtransfusion bei Neugeborenen mit nicht auf Rh-Im-

munisierung beruhender Hyperbilirubinämie angezeigt ist, wurden alle in Uppsala während der Jahre 1957 und 1958 geborenen Kinder in Hinblick auf das Auftreten von Hyperbilirubinämie und neurologischen Symptomen beobachtet. Bei einer aufeinanderfolgenden Serie von 95 ausgetragenen Kindern wurde eine Austauschtransfusion bei jedem zweiten Kind durchgeführt, wenn das Serumbilirubin 20 mg/100 ml erreichte. Im Alter von 3-4 Monaten wurde keinerlei Unterschied zwischen den behandelten und den nichtbehandelten Kindern festgestellt. Keines zeigte neurologische Anomalien, die mit der Hyperbilirubinämie in Beziehung gebracht werden könnten. Eine Austauschtransfusion wurde ebenfalls bei 23 Frühgeburten durchgeführt, bei denen der Serumbilirubinspiegel 15-20 mg/100 ml überstieg. Auch von diesen Kindern zeigte keines nach 3-4 Monaten irgendwelche Symptome neurologischer Anomalien, im Gegensatz zu den Befunden der Jahre 1954-55, als 6 prämatüre Kleinkinder an Kernikterus starben.

Indicaciones para la transfusión recíproca en recién nacidos con hiperbilirrubinemia no debida a la inmunización Rh

A fin de esclarecer la cuestión de cuando resulta indicada la transfusión recíproca en recién nacidos con hiperbilirrubinemia no debida a la inmunización Rh, se observaron todos los

niños nacidos en Uppsala, en 1957 y 1958, con respecto a la existencia de hiperbilirrubinemia y síntomas neurológicos. Tomando una serie consecutiva de 95 niños de término, se realizó la transfusión recíproca en uno de cada dos niños cuya serobilirrubina alcanzaba los 20 mg/100 ml. A la edad de 3 a 4 meses, no se encontró ninguna diferencia entre los niños tratados y los no tratados; ninguno presentaba anormalidades

neurológicas que pudieran relacionarse con la hiperbilirrubinemia. También se realizó la transfusión recíproca en 23 prematuros en los que el nivel de la serobilirrubina rebasaba los 15 a 20 mg/100 ml. Ninguno de ellos presentaba signos de anormalidades neurológicas a la edad de 3 a 4 meses, contrario a los hallazgos de los años 1954-55, cuando 5 prematuros murieron de ictericia nuclear.

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Studies on Osteopetrosis. III

Roentgenological and Pathologic-anatomical Investigations on Some of the Bone Changes

by B. ENGFELDT, C.-M. FAJERS¹, H. LODIN and M. PEHRSON

Osteopetrosis (Marble bone disease, Marmorknochenkrankheit, Albers-Schönberg's disease) is a skeletal dystrophy of unknown origin. It is characterized by generalized, diffuse, pronounced osteosclerosis with great brittleness of the bones—hence the name osteosclerosis fragilis generalisata—and frequent spontaneous fractures. Owing to the retardation or partial or total failure of the resorption and formation of the new bone, the marrow cavity develops defectively.

The condition is often congenital, with a strong familiar tendency. Several types may be distinguished, one more malignant affecting children and characterized by profound anaemia, one more benign and often not detected until much later in life. Investigations into the metabolism of calcium suggest that there is no primary disturbance of mineral metabolism. The most widely accepted theory of the cause of osteopetrosis is that there is diminished osteoclastic activity with retarded or wholly inhibited resorption of bone, resulting in the building up of the inner parts of the enchondral bone by calcified cartilage and primitive bone.

The present paper is devoted to an account of the morphological basis of some of the roentgenological changes in the bone typical of osteopetrosis, and to a consideration of the process that may be behind these changes. The account is based on the material of 4 patients (see Part II, Sjölin, Acta Pædiat; 48: 529, 1959) followed up over a long period, one of whom died and was examined post mortem.

Case Histories. (see Acta pædiat. 47: 279, 1958 and 48: 529, 1959).

Case 2. Necropsy (Fajers). The endocrine organs (hypophysis, thyroid, parathyroids, adrenals, pancreas and testes) were normal (both microscopically and macroscopically). Almost all lymph nodes (cervical, axillary, supra- and infraclavicular, mediastinal, mesenteric, para-aortic, pelvic, inguinal and popliteal) were slightly to moderately enlarged, and mottled reddish brown in colour. The thymus was not enlarged or of abnormal colour. The liver (950 g) was rather pale and slightly yellow. The kidneys (230 g) and urinary tracts were normal. The other organs were apparently normal.

The brain (460 g) had pinkish meninges with slightly injected vessels, and there was a thrombus in the right transverse sinus and longitudinal sinus. Bacteriological cultures from the meninges and the cutaneous fistula to the maxillary sinus revealed the presence

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of staphylococci. The brain was normal. The optic nerves were strikingly atrophied.

Skeletal system. The skull was very thick, and sclerotic. In the region of the sutures the thickness was 5 mm and at the parietal tuberosities 15 mm. The normal pattern of the diploë was lost, but the bone was arranged in obvious layers parallel to the surface. The anatomical features of the base of the skull were markedly coarsened, and the optic foramina were considerably narrowed. The body of the mandible was greatly thickened, and measured at the mid-line 25×30 mm. The alveolar processes were thickened. No teeth were visible, but on section they were found a few mm under the surface of the bone. (A more detailed odontological account of the mandible and teeth is being prepared in collaboration with Borggren.) The pelvic bones and vertebrae were sclerosed. The ribs showed inverted angulation at the angle. The bony ribs were sclerotic, the cartilages were normal. The sternum and manubrium were also sclerotic and moderately thickened. The medullary cavity of the long bones (humerus, ulna, radius, femur, tibia, fibula, clavicle, metacarpal, and metatarsal and carpal and tarsal bones) was filled with sclerotic, calcified tissue. The cortex was also harder than normal, and often also thicker. The metaphyses, especially of the longer bones, and particularly the upper metaphysis of the tibia, were broadened.

Cause of death, thrombosis of the longitudinal sinus and the right transverse sinus and staphylococcal meningitis.

Roentgenological Investigations

All 4 cases showed skeletal changes typical of osteopetrosis, already well-known and described (Schinz, Baensch, Friedl, and Uehlinger, 1952). We shall therefore not give an account of these changes, but will only discuss some other features of the roentgenological picture in the light of the necropsy findings in the patient who died.

Changes not previously discussed in detail in the literature were present in metacarpal, metatarsal, and other bones in Cases 1-3 (Figs. 1, 2, 3, 4, 5 and 7). The typical change is characterized by the presence at or near the centre of the "marrow cavity" of an "endobone". This was distinguished from the more or less sclerotic cortex by an apparently normal degree of calcification and by the presence of a rudimentary marrow cavity (Figs. 1, 2, 3, 4, 5 and 6).

In Cases 1 and 3 it is possible to trace the development of these changes. In Case 1 the metatarsal and metacarpal bones showed diffuse sclerosis as early as 7 weeks of age. At 5 months a thinner layer of nonsclerotic bone was seen surrounding the central patch of sclerosis in the metacarpals (Fig. 1). At 18 months of age this patient showed fully developed "endobones" of the same appearance as in Fig. 3. In Case 3 the first roentgen films were made at 4 months of age, and show a stage (Fig. 2) roughly corresponding to the 5-month picture in Case 1 (Fig. 1). Thus the bones contained conical areas of sclerosis, the bases towards the metaphyses, the apices meeting at the middle. These cones were surrounded by bone of "ordinary" calcium content. — Outside this zone there developed later apparently sclerotic bone, the "endobone" thus being separated from this. Subsequent examination at $5\frac{3}{4}$ years of age thus revealed fully developed "endobone" (Fig. 3). The length of the endobone was the same as that of the conical areas of sclerosis in Fig. 2. Similar changes were also noted in the tibia and fibula of Case 2 (Fig. 7).

Post mortem roentgen examination of the metatarsal and metacarpal bones was carried out in Case 2 (Figs. 4 and 5).

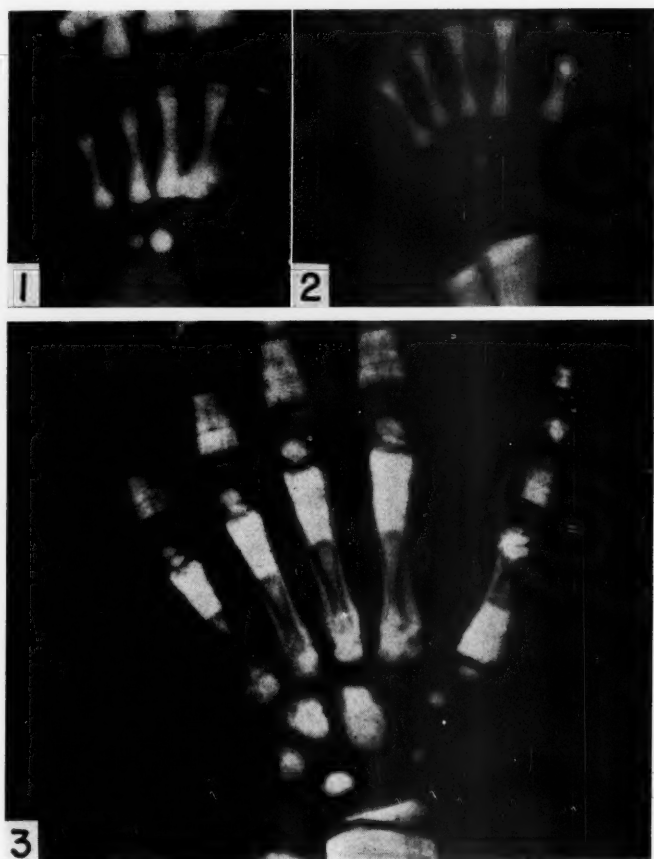


Fig. 1. Case 1, 5 months of age. The central area of sclerosis in the metacarpals is surrounded by a thinner layer of nonsclerotic bone. Transverse bands are seen proximally and distally.

Fig. 2. Case 3, aged 4 months. Within the metacarpals are seen conical areas of sclerosis, the bases lying towards the metaphyses. Non-sclerotic bone is seen surrounding these, especially at the level of the middle of the diaphysis.

Fig. 3. Case 3, aged 5 years and 9 months. A fully developed "endobone" is present within a rudimentary "medullary cavity". The length of the "endobone" is equal to that of the sclerotic area seen at 4 months (Fig. 2).

Transverse section of a metacarpal bone shows the eccentric position of the "endobone" within the bone (Fig. 6). It is separated from the cortex by a less opaque zone (bone of normal calcium content or rudimentary marrow cavity, Fig. 4, 5 and 6). In Case 1 at 7 weeks of age a generalized

diffuse sclerosis of the long bones with no signs of transverse or longitudinal striation was detected. There was some broadening of the metaphyseal ends of the bone, with hollowing and irregularity of the contour, as in *rickets* (Fig. 8). Re-examination at 6 months of age revealed a new, several-

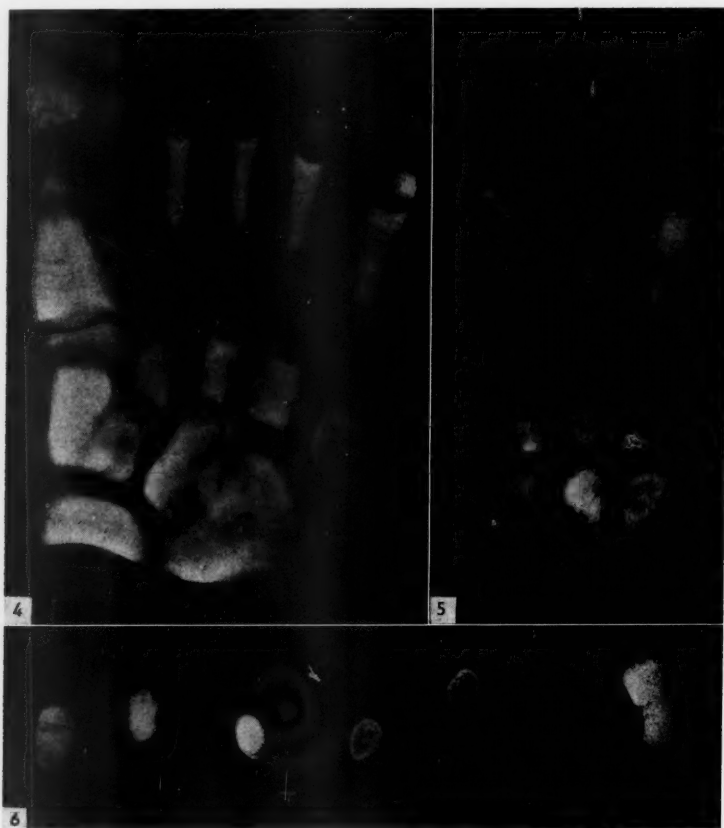


Fig. 4. Case 2, 11½ years. Post-mortem radiogram of the metatarsals. Typical "endobones" are present. Metatarsal V is also shown in Fig. 28.

Fig. 5. Case 2, 11½ years. Post-mortem radiogram of metacarpals, showing typical "endobones". Metacarpal IV was fractured during preparation. Metacarpal II is shown in transverse section in Fig. 6. See also Fig. 27.

Fig. 6. Case 2, 11½ years. Post-mortem radiogram of metacarpal II in transverse section. The eccentric position of the "endobone" is seen in no. 4 from the left. It is separated from the cortex by non-sclerotic bone or rudimentary medullary cavity. Section no. 4 is also shown in Fig. 27, and section no. 5 in Fig. 35.

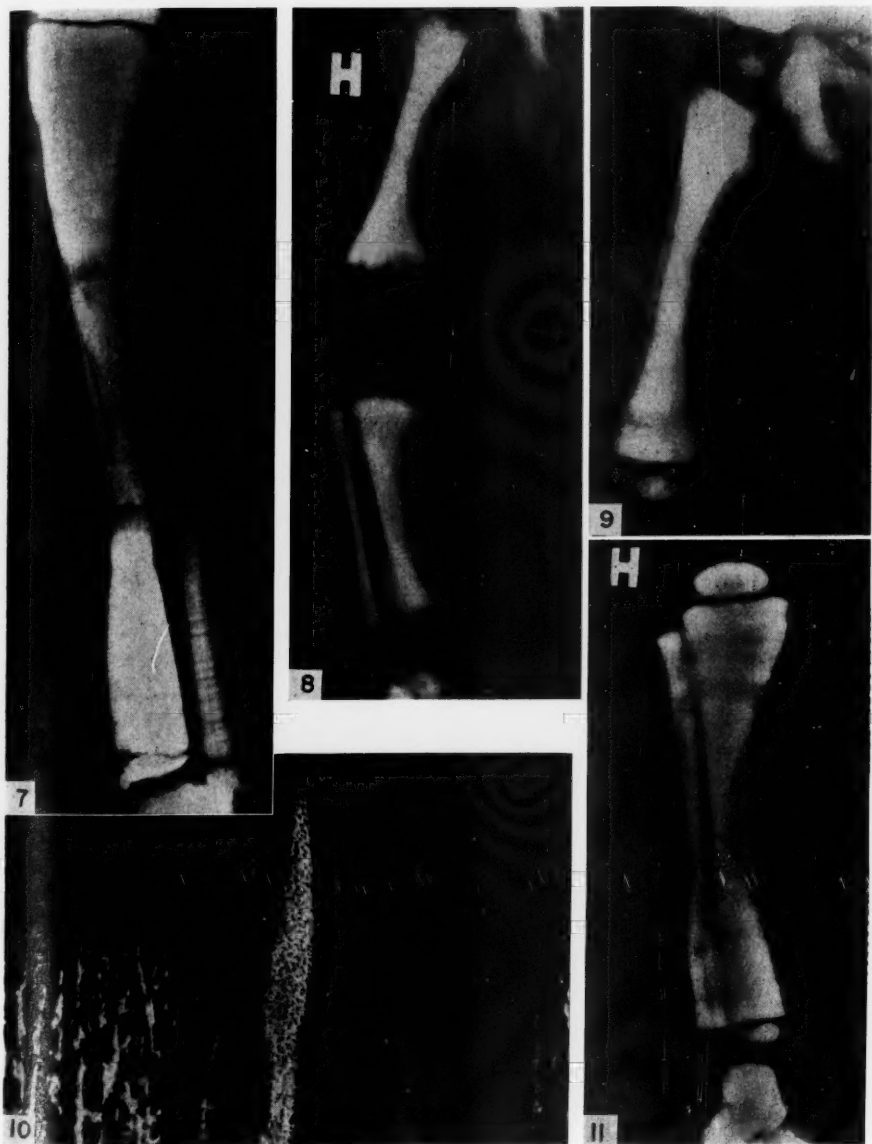
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Fig. 7. Case 2, 11½ years. Left tibia and fibula, showing fully-developed "endobone" within the diaphyses. Typical transverse and longitudinal striations are seen in the metaphyses. See also Figs. 10 and 34.

Fig. 8. Case 1, aged 7 weeks. Diffuse sclerosis is present within the right femur, tibia and fibula, the ends of the metaphyses being broadened and frayed as in rickets.

Fig. 9. Case 1, aged 6 months. Laminated periosteal deposits and well-formed metaphyses are seen in the right femur. Healing rickets. Transverse striations are seen in the metaphyses. The length of the diaphyses between the transverse bands is the same as that of the femur at 7 weeks (Fig. 8).

Fig. 10. Case 2. Microradiogram of the knee-joint metaphysis of the tibia, in the region of the longitudinal striations to the left in Fig. 7. The dark area at the top is the epiphyseal plate. To the left



and right can be seen the radio-opaque medullary bone, arranged in columns from the growing region. In the middle can be seen fibrillar bone extending up through the epiphyseal plate (see also Fig. 34) \times c. 25.

Fig. 21. Case 1, aged 18 months. Laminated periosteal deposits and transverse bands are seen in the right tibia. The length of the diaphyses between the innermost transverse bands is equal to that of the tibia and fibula at 7 weeks (see Fig. 8).



Fig. 12-16. Case 3. The development of transverse and longitudinal striations at the distal ends of radius and ulna. At 4 months (Fig. 12) there is diffuse sclerosis with no clear striations. At 3 years (Fig. 13) there is marked transverse striation and a few longitudinal striations. Figs. 14-16 show the striations at 4, 5 and 7 years of age.

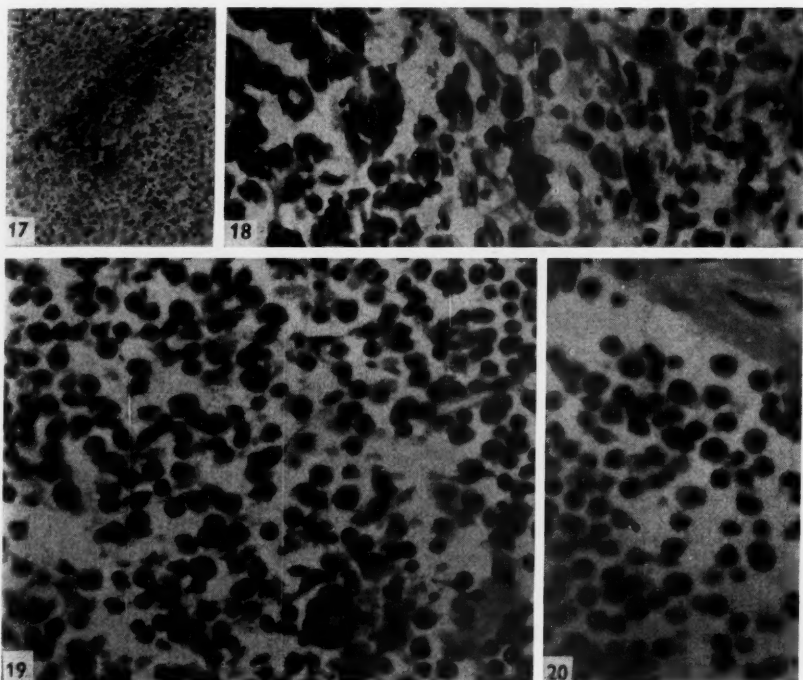


Fig. 17. Case 2. Abundant haemosiderin deposits in a lymph node. Schneider's Berlin blue stain. $\times 60$.

Fig. 18. Case 2. Abundant haemosiderin deposits in a lymph node, partly taken up by macrophages. Haematoxylin-Eosin. $\times 230$.

Fig. 19. Case 2. Extramedullary haematopoiesis in a lymph node. Note the megakaryocyte. Haematoxylin-Eosin. $\times 230$.

Fig. 20. Case 2. A blood vessel from the lung showing large numbers of immature cells. Haematoxylin-Eosin. $\times 230$.

layered periosteal reaction extending over the entire diaphysis and into the adjoining metaphyses (Fig. 9). Transverse striations were now present. The metaphyses were clearly and smoothly delineated from the epiphyseal cartilage. The rickets picture was thus now resolving. New examination at 18 months of age revealed further periosteal deposits, and transverse striations in the metaphyses (Fig. 11).

Repeated roentgen examination of Case 3 has been made over a now nearly 6-year period. A good idea of the development of the *transverse lines* that are seen in the

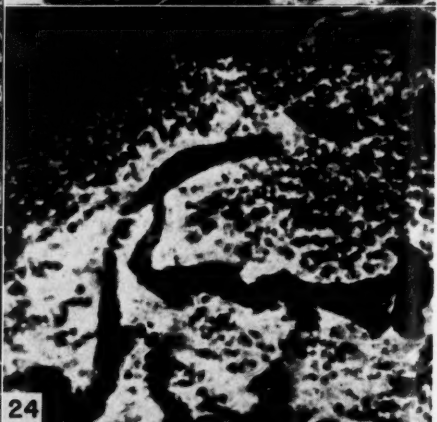
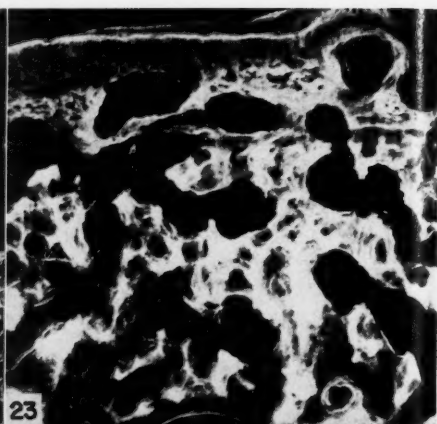
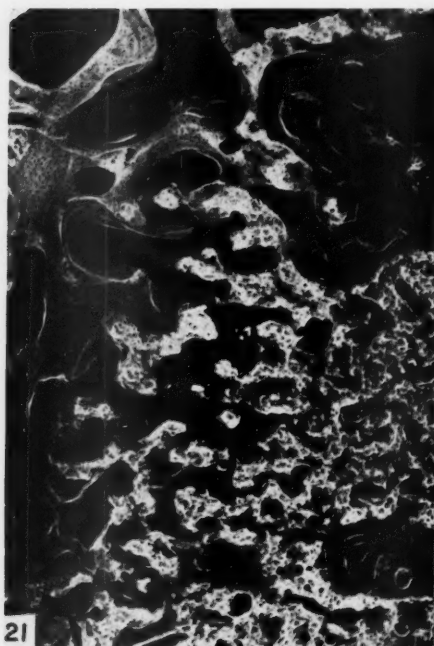
metaphyses of the long bones can now be obtained (Figs. 12-16). Similar striations were also observed in the metacarpal and metatarsal bones (Figs. 3, 4 and 5), in the metaphysis adjoining the epiphyseal centre.

The *longitudinal striations* are also clearly seen in Figs. 7 and 13-16.

Morphological Investigations

Technique

Tissue specimens were fixed in neutral buffered 10% formaldehyde. For histological preparation of the soft tissue the specimens were embedded in paraffin and the sections



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stained with haematoxylin and eosin, van Gieson's stain, and in many cases with Schneider's Berlin blue to demonstrate free iron.

For histological preparation of the hard tissue the specimens were fixed as above, and cut into suitable pieces which were decalcified in a solution of equal parts of 20% monosodium citrate and 44% formic acid (pH 1.9). This fluid was changed daily until the tissue had softened, which was usually after 15–20 days. The pieces were then passed through alcohol and methyl benzoate and embedded in paraffin, and then sectioned and stained with haematoxylin and eosin and van Gieson's stain.

For X-ray microscopy suitable pieces of undecalcified bone were sawed out and passed through alcohol and increasing strengths of methylmethacrylate monomer in alcohol and finally in 100 per cent partially polymerized methylmethacrylate which was then allowed to harden. The specimens embedded in plastic were then cut by means of a special circular saw into 1–2 mm-thick planoparallel "sections" which were ground down to a thickness of 100–150 μ by means of carborundum paper of increasing fineness.

Some of the material for X-ray microscopy was prepared by grinding without preliminary embedding in plastic; sections of about 500 μ in thickness being first cut with an exceedingly thin circular saw, and then

ground in alcohol to about 100 μ on ground glass.

The X-ray microscopy was carried out with a Philips' diffraction unit, using copper radiation filtered through nickel. With the voltage used the major part of the radiation corresponded to 1–3 Å. Within this wavelength range more than 95% of the absorption of bone tissue is due to the mineral salts. The different densities observed in the image thus reflect differences in concentration of mineral salts. The image obtained was at unit magnification and was enlarged by photomicrography.

A special camera with a focus to emulsion distance of 30 cm was used. The specimen was placed in immediate contact with a photographic emulsion of extremely fine grain (Kodak spectroscopic plate no. 649 resolving power about 1000 lines per mm). After exposure, the plate was developed in Kodak D 19 B and the image enlarged by photomicrography.

Findings

In all 4 cases there was splenic tissue for assessment. Apart from infarcts in Case 3 all the spleens were histologically similar, and showed moderate to marked erythro- and myelopoiesis. Megakaryocytes were present in varying numbers, but fairly large quantities of haemosiderin

Fig. 21. Microradiogram of the clavicular diaphysis. The whiter areas represent highly mineralized, calcified cartilage and primitive bone, typical of the medullary bone of osteopetrosis. In the upper left-hand corner are seen parts of reconstructed lamellar bone. In the upper right-hand corner can be seen the suggestion of Haversian systems and a few can also be seen in the medullary bone in the lower right-hand corner. \times c. 30.

Fig. 22. Microradiogram of a rib. The periosteal bone consists largely of highly mineralized bone with numerous lacunae of osteocytes. In the centre there is a large resorption cavity that is being filled out by osseous tissue. Haversian systems mineralized in varying degree are seen in the upper right-hand corner. \times c. 50.

Fig. 23. Microradiogram of a rib. In the lower part can be seen medullary bone, which is for the most part highly, though in rather varying degree, mineralized. Along the upper edge there is a highly mineralized cementing line, and below this an area of lamellar, immature bone with abundant osteocyte lacunae. In the upper right-hand corner can be seen a Haversian system. \times c. 65.

Fig. 24. Microradiogram of a rib. Fibrous bone, in the lower right-hand corner highly mineralized, in the upper part slightly mineralized. \times c. 50.

Fig. 25. Microradiogram of the middle of the centre of ossification in a metacarpal epiphysis. At the middle of the field there is a medullary cavity surrounded by a narrow zone of highly mineralized bony tissue. The tissue outside this, which appears "worm-eaten", consists of slightly mineralized cartilage with cartilage capsules. \times 80.

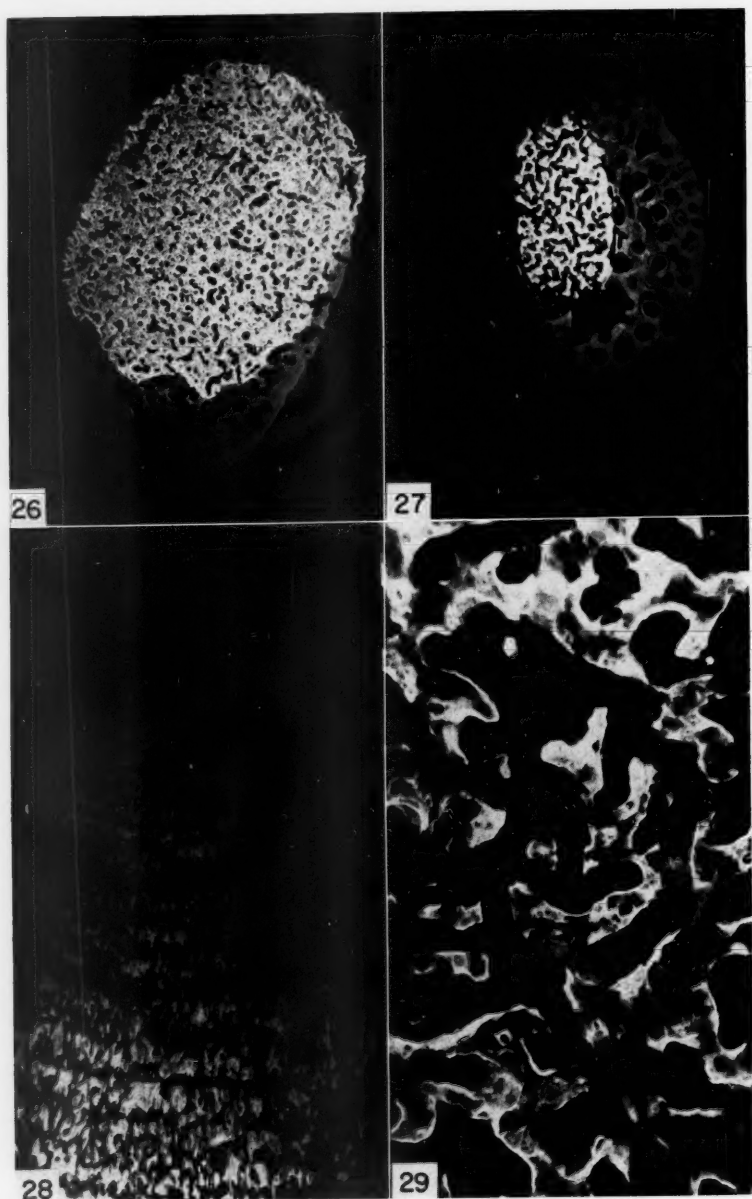


Fig. 26. Case 2. Microradiogram of a metacarpal metaphysis. The central, somewhat eccentrically placed medullary bone is distinct from the thin sheath of more normal periosteal bone, owing to its density. In the latter can be seen cementing lines and Haversian systems. $\times 18$.

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were seen in the macrophages in Case 2 only.

The liver specimen (needle-biopsy) from Case 3 contained isolated groups of haemopoietic cells and was otherwise normal. In Case 2, all major organs and most of the skeleton were examined at necropsy.

Case 2. The liver, which apart from slight fatty changes was normal, contained fairly large quantities of blood-forming parenchyma, chiefly in portal and periportal connective tissue. The normal architecture of the *lymph nodes* was to a large extent obliterated, the tissue being replaced by blood-forming parenchyma (Fig. 19). Those lymph nodes who were macroscopically brown showed much haemosiderin (Figs. 17 and 18). No extra-medullary blood formation was seen in the *kidneys*. Large numbers of primitive, nucleated blood-forming cells were seen in the vessels of all organs (Fig. 20).

The following bones were examined: sternum, ribs, vertebrae, patella, clavicle, humerus, radius, ulna, metacarpals, femur, tibia, fibula, metatarsals (epi-, meta- and diaphysis), and the bones of the skull. Cartilage from the trachea, ribs, and sternum was normal in structure. The histological and X-ray microscopical findings in the intra-cartilaginous bone were similar throughout, and individual bones will not therefore be described separately. A general description of the characteristic findings follows.

1) *Metaphyses*. The usual vesiculation of the cartilage cells from the epiphyseal plate, the individual cells being arranged in columns, was seen (Fig. 34). The cartilage became calcified in the zone of provisional calcification zone and became penetrated by vessels. Immediately proximal to the zone of provisional calcification could be seen the

strips of newly-formed bone covering the calcified ridges of cartilage. So far the picture was the same as that seen under normal conditions. The calcified interstitial substance persisted in greater degree than normal, and rows of vesicular cartilage cells could even be seen far down the diaphyses (Figs. 30, 31 and 34). X-ray microscopy revealed that many of these columns of cartilage cells were surrounded by calcified interstitial substance forming what is usually referred to as medullary bone. Osteoblasts and osteoclasts were seen in the region of the invading capillaries, connective tissue, and new bone. It was not unusual in longitudinal sections of the metaphyses to see strands of more normal bony tissue lying at right angles to the longitudinal axle of the section (Fig. 33), and sometimes also small areas of resorption, primitive marrow cavity, very often arranged parallel to the epiphyseal plate (Fig. 31). Coarser, longitudinally running vessels surrounded by abundant connective tissue and coarse fibrillar immature bony tissue in long continuous strands or spurs were sometimes seen in the metaphyses. These vessel-containing spaces stretched towards the diaphyses in the medullary bone and sometimes also upwards and through the epiphyseal plate (Figs. 10 and 34).

2) *Epiphyses*. The picture was strongly reminiscent of that seen in the metaphyses. Adjacent to the cartilage there was a similar zone of calcification invaded by vessels and connective tissue between the cartilage cells, and showing formations of thin layers of bony tissue. Osteoblasts and osteoclasts were present. It was striking that there was abundant resting hyaline cartilage at the middle of the old ossification centres (Fig. 32). This cartilage was calcified and showed varying degrees of mineralization (Figs. 25 and 29). The formation of spongy bone was

Fig. 27. Case 2. Microradiogram of metacarpal II (transverse section no. 4, Fig. 6). Here the periosteal bone is more abundant, with numerous, highly mineralized cementing lines and large numbers of Haversian systems, some of them normal. $\times 18$. Cf. Fig. 35.

Fig. 28. Microradiogram of metatarsal V, in longitudinal section. The dark band in the upper part corresponds to the epiphyseal plate. The transverse striations are clearly seen in the metaphysis. $\times c. 10$.

Fig. 29. Microradiogram of an epiphyseal centre of ossification. $\times 75$. Cf. Fig. 32.

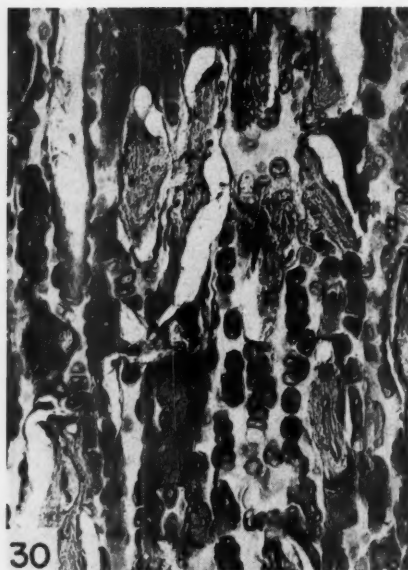


Fig. 30. Case 2. Longitudinal section of medullary bone from the tibial diaphysis. The columnar arrangement of the cells from the growth zone of the cartilage is still retained. Haematoxylin-Eosin. $\times 60$.

Fig. 31. Case 2. Longitudinal section of medullary bone immediately under the epiphyseal plate of a metacarpal. Humorous resorption cavities lying at right angle to the longitudinal axis of the bone. In the cavities connective tissue, osteoblasts, and osteoclasts are seen. Haematoxylin-Eosin. $\times 60$.

Fig. 32. Case 2. At the middle of an epiphyseal centre of ossification can be seen abundant cartilage and resorption cavities with osteoclasts and osteoblasts. Haematoxylin-Eosin. $\times 60$.

Fig. 33. Case 2. Longitudinal section of a metacarpal diaphysis showing one or two transverse bands of fairly normal bony tissue in the medullary bone and the suggestion of a marrow cavity. Haematoxylin-Eosin. $\times 4$.

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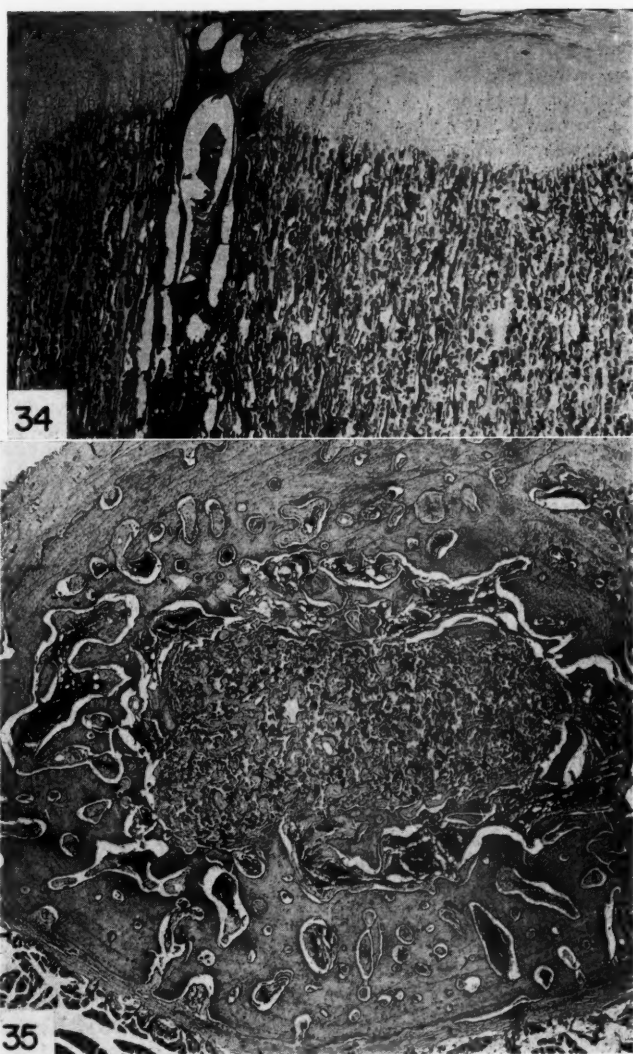


Fig. 34. Case 2. Longitudinal section through the upper tibial metaphysis (see also Fig. 7) with a perforating vessel surrounded by connective tissue and a few narrow spurs of bone. Cf. the micro-radiogram of Fig. 10, showing the same region. Haematoxylin-Eosin. $\times 8$.

Fig. 35. Case 2. Transverse section of metacarpal II, corresponding to section 5, Fig. 6. The medullary bone is surrounded by marrow cavities separating it from the more normal periosteal bone. Haematoxylin-Eosin. $\times 12$.

markedly retarded or absent, but resorption cavities resembling primitive marrow cavities with connective tissue and cells were occasionally seen within limited areas.

3) *Diaphyses.* Instead of the normal marrow cavity there was in every instance a column consisting of calcified cartilage and endochondral bone of the type seen in the metaphyses (Figs. 26, 27, 28, 33 and 35). Several zones could often be distinguished in this compact bone. Immediately under the periosteum there was a layer of lamellar bone with a varying number of circularly arranged cementing lines and fairly large numbers of osteocytes (Figs. 27 and 35). This was followed by compact bony tissue with partially abnormal Haversian systems. Internal to the compact bone a new layer of lamellar bone with circularly arranged cementing lines (here often less obvious) could sometimes be distinguished, and within this another layer of Haversian bone. Large resorption cavities with connective tissue and haemopoietic cells could occasionally be seen between these layers (Figs. 22 and 35). The outer parts of the compact bone often appeared microscopically "normal", the number of atypical Haversian systems increasing towards the centre. At the centre too, the bony tissue was sometimes more primitive, coarsely fibrillar and cellular. The periosteal bone formation in the diaphyses often varied at different parts of the circumference, with the result that several layers were often present at one site, while other areas showed only one layer of lamellar, concentric bone sometimes entirely without Haversian systems. Thus the medullary bone replacing the marrow cavity lay in some places only a millimetre below the periosteum, whereas in others it was about a centimetre below.

4) *Membranous bone.* In the ossification centres the picture was the same as that seen in the diaphyses, that is, alternating layers of bone, outermost lamellar bone with cementing lines and within it a layer containing atypical Haversian systems, followed by another layer of lamellar bone, etc.

Over and above what has been described,

X-ray microscopy showed that the medullary bone had a high mineral content the degree of calcification exceeding the most heavily mineralized structures in normal compact bone. However, the distribution of mineral salts in the medullary bone was observed to be uneven: areas containing remnants of cartilage cells were as a rule less heavily mineralized than surrounding tissue. Small bridges of bone were encountered, which showed a degree of mineralization comparable with compact bone (Figs. 21 and 23).

It was found that the abundant hyaline cartilage in the epiphyses was mineralized, the calcium content of the interstitial substance being in places equal to that of compact bone (Fig. 25), but for the most part rather lower.

In the compact bone there were large areas showing the normal pattern of calcification. Highly calcified interstitial lamellae were seen, together with apparently normal Haversian systems showing varying degrees of mineralization. In places, however, immature, coarsely fibrillar bony tissue, sometimes only slightly calcified, was seen (Fig. 24), and in these areas Haversian systems of varying appearance were encountered, some atypical with numerous, heavily calcified irregular thin zones coursing through the osteons. Highly mineralized cementing lines were abundant in the compact bone, especially in the regions adjacent to the marrow cavity, and here, too, were seen large numbers of resorption cavities, often with formation of new bone beginning at the periphery.

Discussion

The roentgen series (Figs. 1, 2 and 3) shows that the "endobone" remains roughly the same size. It is built up of remnants of medullary bone, i.e. mainly calcified cartilage with small amounts of unresorbed spongy bone (Figs. 27, 33 and 35). The less opaque zone separating the "endobone" from the metaphyses is matched by transverse bands of lower density.

Crevelde *et al.* (1940) described no "endobone" in the metacarpals of an infant who died at 9 days of age. In Case 1 none were seen at 7 weeks, but the structures were demonstrable at 5 months (Fig. 1). The explanation of this phenomenon may well be that the period of most rapid growth starts during the 1st-5th months of life. Variations in the date of appearance of the endobone may be associated with the date at which the skeletal changes begin to take place. In Laurell & Wallgren's (1920) case, aged 12 years, some of the metacarpals showed largely normal diaphyses with the patterning of spongy bone, even though the cortex was broadened. In our cases, too, these endobones seem to tend to become rarified; probably because this tissue is steadily but very slowly resorbed. The development of the cuff of bone, with successive new-formation and resorption, results however in the gradual reduction in the relative amount of medullary tissue in the diaphysis. On the basis of the morphological findings it would seem likely that the resorption and subsequent reconstruction takes place more readily in the compact than in the endochondral bone. The morphological findings show that the medullary bone is clearly capable of being resorbed, at least within certain areas. In other regions, especially close to the metaphyses, it will persist for a considerable time. Here too, it is possible that resorption might ultimately take place, and marrow cavity with no vestiges of endochondral bone appear within the diaphyses. The periosteal bone formation and reconstruction sometimes takes place only within a certain section of the circumference, and this may be why the endobone is sometimes placed asymmetrically within

the bone. Owing to the varying rates of growth in different metaphyses, the area of endochondral bone formed first will appear to be "displaced" along the long axis of the bone, the amount of displacement varying from bone to bone (Figs. 2, 3, 4, 5 and 6).

The difference in density between the compact and medullary bone (Figs. 5, 26 and 27) undoubtedly accentuates the image of the "endobone". There is much to suggest that the "bone in the bone" previously described by Hinkel & Beiler (1955) is of the same nature. The process in the latter is perhaps more analogous to the case of the longbone metaphyses, and the layering is then more comparable with the transverse striations (Figs. 3, 4, 5, 6, 12, 13, 14, 15 and 16).

As long ago as 1920 Laurell & Wallgren demonstrated *transverse striations* and broad transverse bands of greater density in the metacarpal metaphyses in regions undoubtedly corresponding to "medullary bone" and surrounded by less opaque zones occasionally even showing spongy patterning. Changes similar to those seen in rickets are common in osteopetrosis, and may possibly be responsible for these bands (Figs. 8, 9 and 11). Transverse bands in the metaphyses are not uncommonly encountered in other disease states. The roentgenological bases for these bands or striations is varying density of the bone. This is thought to be due to temporary inhibition of growth of the proliferating cartilage, resulting in horizontal instead of vertical extension of the vessels growing in from the diaphysis. The amount of mineralized tissue will thus be increased locally. Such changes can commonly be related to infections, rickets, toxic states,

etc. Patients with osteopetrosis are highly susceptible to infections, a fact that may be related to the above changes.

A contributory cause of the transverse lines in cases of osteopetrosis may be that the dark (radiologically less opaque) regions represent regions containing numerous resorption cavities with marrow cavity (an expression of a relatively normal process), and the light (radiologically dense) regions bands of medullary, heavily calcified, "osteopetrosis bone" (Figs. 28 and 31). Furthermore, transverse strands of more highly differentiated bone can be detected in different long bones (Fig. 33), crossing the medullary bone at right angles from cortex to cortex, from the epiphyseal plate far down into the diaphysis. This indicates that reconstruction of the bone has indeed taken place, and also that the process responsible for the skeletal disease shows periods of varying intensity.

Concerning *longitudinal striations*, such as are seen for example in the tibia would seem to suggest that the morphological basis for these is persistent, perforating vessels surrounded by connective tissue (Figs. 7, 13 and 16). These vessel-containing spaces may have a depth of up to about one centimetre, at least in the frontal plane. X-ray microscopy and histological investigations show that these vessel spaces sometimes accompany strands of fibrillar bony tissue that may reach as far as the epiphyseal plate (Figs. 10 and 34). In the light of Figs. 10, 28, 30 and 31 the numerous, fine longitudinal lines are undoubtedly due to the persisting columnar arrangement of the cells of the growth zone of the cartilage (Fig. 34) in combination with fine vascular spaces.

Finally, concerning the nature of osteopetrosis, the X-ray microscopic and histological findings would indicate that the condition is not due to absence of osteoclasts, nor does there appear to be a lack of osteoblasts. It would hardly seem possible that osteopetrosis should result from "gradual encroachment of the sclerotic bone on the medullary canal, causing depletion of the bone marrow" (Kneal *et al.*, 1951), but there is much evidence in favour of the view of Weinmann & Sicher and others that there is "failure of bone resorption, which normally increases the diameter of the bone marrow". During the rapid growth that takes place during childhood, resorption of the calcified cartilage and the newly-formed bone evidently does not keep pace with the bone formation. The reason would seem to be a congenital inability to resorb bone. The explanation of this latter phenomenon is unknown. The disturbance in reconstruction of bone takes place at the same time. This may be very marked, at any rate within limited areas (Engfeldt *et al.*, 1955). The occurrence of subclinical fractures which heal spontaneously and of true fractures that heal well (Kneal *et al.*, 1951) indicates the same thing. Here there is thus no complete inability to resorb calcified tissue, but a variation in ability.

As will have been clear from the above, the histological and X-ray microscopical findings suggest that considerable reconstruction, with resorption and new-formation, can take place in certain parts of the compact bone. Clinical roentgenological findings also indicate that the bony cuff in the long bones undergoes continuous reformation and growth, and is of a size corresponding to that normal for the age

in question. With regard to the calcified tissue in the marrow cavity, the rate of reconstruction of the medullary bone is very low, however. The difference between the reconstruction process in the metaphysis, - the area of endochondral bone formation, - and that in the compact bone is that the former also involves resorption of cartilage and calcified cartilage. This latter process is intimately related to the growth of vessels towards the epiphyseal plate from the diaphysis. Several theories regarding the failure of normal resorption of the proliferating epiphyseal cartilage may be put forward. There may be changes in the properties of the cartilage such that it is not broken down properly by the action of capillary growth. Another possibility would be that the capillaries are abnormal or are too few to accomplish the requisite breakdown of cartilage. Evidence in support of the latter alternative is possibly the finding in the medullary bone of cartilage capsules arranged in columns, a feature which is never encountered under normal circumstances when the capillaries perforate the degenerated cartilage capsules in the growth zone. Normally, however, small islets of cartilage interstitial substance can be seen embedded in the spiculae of bone adjacent to the epiphyseal plate. Another finding that might possibly be interpreted as a sign of vascular abnormality is the occurrence of wide penetrating vessels running in the direction of the long axis of the bone, and here and there penetrating the epiphyseal plate. Angiographic studies of the blood supply of the bones in osteopetrosis might throw new light on this problem. On the other hand, calcification of the interstitial substance of the resting cartilage observed in the

epiphysis is a finding that might indicate some abnormality in the structure or metabolism of the cartilage.

The impaired capacity of the tissue to resorb bone is often mentioned in connexion with osteopetrosis. It would perhaps be more fitting to use the term "calcified tissue" instead of "bone", since as has been pointed out in this paper a very essential factor is the impaired capacity to resorb calcified cartilage.

On the basis of the mechanism outlined, in which the primary cause of the impairment of bone resorption is unknown, it is perhaps possible to explain the various forms of osteopetrosis distinguished by Harnapp (1937). In the malignant form, which appears early this failure of resorption is more complete and the spontaneous remissions are absent, few, or brief. These cases are characterized by an almost complete absence of marrow cavity and bone marrow, but show instead more extensive extramedullary haematopoiesis and increased activity in the reticulo-endothelial system, with haemolytic anaemia etc. The patients die early, possibly largely from the "blood disease" or its complications. The benign cases have better capacity for resorbing calcified tissue, or else the process is marked by long, spontaneous remissions (Fairbank, 1948, Kneal & Sante, 1951) during which the medullary cavities and bone marrow become formed. These patients usually show no anaemia, and are often detected fortuitously and at an older age.

Summary

The morphological basis of some characteristic roentgenological findings in malignant, generalized osteopetrosis (marble

bone disease) is discussed in the light of 4 patients, one of whom died and was examined post mortem by X-ray microscopy. The "endobone" seen on radiography of the metacarpals, metatarsals and other long bones and also the morphology of the transverse and longitudinal striations in the metaphyses of the long bones were thus investigated.

The nature of the skeletal changes in osteopetrosis is discussed in the light of the roentgenological and morphological findings. The fact that the inability to resorb mineralized tissue affects the calcified cartilage is stressed, and it is pointed

out that it may be due to abnormalities in the cartilage occurring in this condition or it may be connected with the development of the vascular network of the metaphysis. It is also mentioned that the impaired power of resorption of calcified tissue occurring in osteopetrosis is not constant, spontaneous remissions taking place during which there may be resorption and reconstruction of bone.

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Renal Aspects of Acid Base Control in the Newly Born

1. Natural Development

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The maintenance of a steady pH in the plasma and cells is partly the responsibility of the kidney, and the substances excreted in the urine to regulate the pH are fairly well known in adults, both on normal diets and after provocative doses of acidifying or alkalinizing drugs. The subject was reviewed briefly by Widdowson & McCance (22) and more recently and extensively by Elkinton (4). The interest of the newborn period lies in the recognised immaturity of the kidney in other respects at this age, and the maintenance of a stable internal environment mainly by virtue of the integration of food and growth with renal function. The initial days of starvation in human infants and the specialised diet later, or in other animals from birth, are all part of this. Papers bearing on the subject have been published by McCance & von Finck (14) and more recently by Widdowson & McCance (22) and McCance (12), but there is little else to be found in the literature.

Materials and Methods

Twenty-nine baby boys were studied. Urine was collected from seven of them at the moment of birth, from nine over the first 48 hours after birth and from twenty-six on

the seventh day of life; of the last, sixteen were fully breast-fed and ten had had nothing but a cow's milk preparation (Ostermilk No. 1) from the time they started to take food. The urine collections were made as described by McCance & Widdowson (15), and all specimens were preserved under toluene. Twenty-four hour collection of urine from eleven young men served for the adult comparisons.

The measurement of pH was made with B.D.H. capillators. Titratable acid was determined by titrating with 0.01N NaOH to pH 7.4 with phenol red as indicator, and to pH 8.0 with phenol phthalein. Ammonia was estimated by Conway's (1950) method, or by distillation in a micro-Kjeldahl apparatus at pH 8.0. Total nitrogen was determined by the micro-Kjeldahl technique, after digestion with H_2SO_4 with copper selenite as catalyst. For creatinine, phosphorus and inorganic sulphur slight modifications of the methods described by Hawk, Oser & Summerson (9) were used. For chloride in the larger samples of urine passed on the 7th day Volhard's method (9) was used, but for the small volumes passed at birth and on the first and second days Sendroy's (20) method was preferred.

Results

Table 1 shows the average composition per 100 ml or per l of the urine secreted by babies before and during the first two days after birth. The latter urines contained a

TABLE 1. *Composition of the urine secreted by babies before birth and during the first 2 days afterwards.*

(Averages and standard deviations)

	Formed <i>in utero</i> and passed at birth	1st day after birth	2nd day after birth
Number of samples	7	9	9
pH	6.3 \pm 0.36	5.8 \pm 0.41	5.8 \pm 0.32
Titrateable acid mEq/l pH 7.4	0.41 \pm 0.23	10.2 \pm 7.0	11.8 \pm 5.4
8.0	0.66 \pm 0.23	14.2 \pm 7.2	16.1 \pm 5.4
Ammonia mEq/l	4.55 \pm 2.13	30.1 \pm 7.6	34.0 \pm 14.7
Percentage of titrateable acid (pH 7.4) + ammonia excreted as ammonia	89 \pm 5.8	76 \pm 10.6	74 \pm 9.7
P mg/100 ml	0.11 \pm 0.13	1.87 \pm 1.51	11.2 \pm 13.0
Creatinine mg/100 ml	16.1 \pm 7.0	82 \pm 4.7	81 \pm 4.4
Total N mg/100 ml	74 \pm 35.8	459 \pm 99	640 \pm 148

TABLE 2. *Acid excretion by babies during the first week of life and by adults.*

(Averages and standard deviations per kg per 24 h)

	Babies					Adults
	Day 1	Day 2	Day 7			
			Breast fed	Fed cow's milk formula		
Number of samples	9	9	16	10	11	
Urine volume ml	8.5 ± 3.5	12.4 ± 5.5	76 ± 17	69 ± 13.5	20 ± 3.2	
pH	5.8 ± 0.41	5.8 ± 0.32	6.2 ± 0.96	5.9 ± 0.28	5.8 ± 0.37	
Titrateable acid mEq	0.073 ± 0.037	0.14 ± 0.093	0.15 ± 0.113	1.01 ± 0.26	0.64 ± 0.125	
pH 7.4						
8.0	0.11 ± 0.044	0.19 ± 0.087	0.20 ± 0.123	1.23 ± 0.21	0.73 ± 0.125	
Ammonia mEq	0.26 ± 0.12	0.37 ± 0.12	0.56 ± 0.15	0.72 ± 0.13	0.80 ± 0.14	
Percentage of titrateable acid (pH 7.4) + ammonia excreted as ammonium salts	76 ± 10.6	74 ± 9.7	82 ± 12.6	42 ± 4.8	56 ± 5.3	
P mg	0.12 ± 0.03	1.71 ± 2.30	0.32 ± 0.19	38 ± 9.7	16.5 ± 3.2	

higher concentration of total nitrogen and creatinine and were therefore presumably more concentrated than the former. The pH was lower after birth and the ammonia decreased as a proportion of the surplus anions not combined with fixed base. These surplus anions are equivalent to the total amount of hydrogen ions and ammonium salts i.e. the titrateable acid + ammonia. Hanon, Coquoin & Pignard (7) found no ammonia or phosphate in the urine formed

in utero, but urines collected in this investigation have always contained some, and the percentage of the surplus anions excreted as ammonium salts was high by adult standards. This was probably not due to a high rate of excretion of ammonia, but to the very small excretion of phosphates (see later), for without phosphates the titrateable acidity of the urine must be low unless it contains abnormal constituents. At this time of life most of the

TABLE 3. *Urinary excretion of nitrogen, sulphur and electrolytes by babies during the first week of life and by adults.*

(Averages and standard deviations per kg per 24 h)

	Babies				
	Day 7				Adults
	Day 1	Day 2	Breast fed	Fed cow's milk formula	
Total N mg	38.9 ± 18.4	75.4 ± 25.9	108 ± 21.1	229 ± 12.0	207 ± 24.2
Creatinine mg	6.4 ± 3.5	8.8 ± 3.4	13.2 ± 7.9	12.1 ± 2.5	21.9 ± 4.4
Inorganic S mg	3.4 ± 1.7	4.9 ± 3.4	6.0 ± 2.1	19.1 ± 7.1	19.2 ± 4.2
K mEq	0.36 ± 0.14	0.45 ± 0.24	0.95 ± 0.65	2.11 ± 0.80	1.05 ± 0.13
Na mEq	0.25 ± 0.07	0.22 ± 0.17	1.78 ± 1.29	2.68 ± 0.53	2.66 ± 0.54
Cl mEq	0.43 ± 0.18	0.36 ± 0.22	2.08 ± 1.00	2.99 ± 0.87	2.80 ± 0.62

titratable acidity is due to the buffering action of organic acids (1, 14, 22, 24), of which amino-acids and citric acid are generally the most important. On the seventh day of life breast fed infants were found by Stanier (21) to be excreting an amount of citric acid which averaged 33 mg/kg/24 hrs, and was more than the amount excreted by the adults in this series.

Table 2 shows the pH and average of the quantities of water, titratable acid, ammonia and phosphorus excreted by each infant during the first and second 24 hours of their lives, and also the amounts of these substances excreted by babies having breast milk or a cow's milk preparation on the 7th day after birth. The results are expressed per kg per 24 hours to give some idea of the quantities being handled by the kidneys, and comparable figures are given for the adults. In so far as they are comparable, the quantities of ammonia excreted are in general agreement with those given by Hungerland & Schulz (11). Table 3 shows the excretion of nitrogen, creatinine, inorganic sulphur, potassium, so-

dium and chloride by the same babies and adults and the results are expressed in the same way.

On the first day of life the amount of phosphorus excreted was extremely small and the titratable acidity in the urine correspondingly so, although the pH was as low as 5.8. The amount of ammonia was also small by adult standards, but, as already indicated, it accounted for a higher percentage of the ammonia + titratable acid than it normally does in adult urine. By the second day the amount of phosphorus excreted had risen to 1.7 mg. The total nitrogen had also risen (Table 3), but to a much smaller extent. Both results were due mainly to starvation and the catabolism of tissue solids (18, 23), and both can be accentuated by a fall in the environmental temperature or anything else which increases tissue catabolism above the low level to be expected at this time of life (13, 17, 18, 19). Since, however, these were normal healthy infants, the amount of phosphorus excreted was small, and the sum of the ammonia and titratable acid was still less than the figure found for the

adults, and ammonia still accounted for a higher percentage of it.

By the seventh day the breast fed babies were getting about 450 ml of human milk per day, which contained 7.5 g of protein or about 2.5 g/kg, and they were passing three to four times as much urine per kg of body weight as the adults. Their excretion of sulphur averaged 6.0 mg/kg/day and the quantity of surplus anions excreted without fixed base had risen to about half the adult level, but since the infants were still excreting little or no phosphates, most of these anions were covered by ammonia. The pH of the urine was a little higher than it had been on the first two days, and the increased volume of the urine may have been one reason for this (3, 10). The infants on a cow's milk preparation presented a somewhat different picture. The higher intake of protein provided much more sulphur-containing amino-acids than the infant could assimilate. The excess, excreted as sulphates, came to about 19 mg/kg/day, which was the same amount as the adults excreted, and this helped to create a demand for more ammonia and (or) free H ion excretion. The latter was made possible by the amount of phosphates in the milk, which were also considerably in excess of requirements. Consequently there was nearly three times as much ammonia plus titratable acid in the urine of these babies as there was in the urine of those which were breast fed, and ammonia, although present in somewhat larger amounts, accounted for a much smaller percentage of the total. The excretion of titratable acid and ammonia by adults depends to a large extent upon the protein intake, and the young

men who served as the adult controls in this experiment were taking more protein in their food than the adults previously studied by Widdowson & McCance (22), so that their excretion of surplus anions was also higher. Even so, the amount of ammonia plus titratable acid excreted by the bottle fed infants exceeded the amounts excreted by the adults.

A few infants have been investigated when they were eight months to one year old, and at this age they were again excreting more titratable acid plus ammonia than adults. This is explicable in terms of their protein intakes, rate of metabolism and growth. A child one year of age consumes about 3.5 g of protein/kg/day which is about three times as much as an adult, but only 8 or 10 per cent of it is used for growth in contrast to the 50 per cent or so retained by the breast fed baby on the seventh day of life, so that correspondingly more sulphate requires to be excreted.

The excretion of creatinine was higher on the seventh day of life than it was on the first and second, but it was no higher in the bottle fed than in the breast fed babies, in spite of the difference in their nitrogen excretions. The creatinine excreted by the adults was about twice as high per kg of body weight as the amount excreted by the babies on the seventh day.

The fall in excretion of sodium and chloride and rise in excretion of potassium on the second day confirms and extends previous observations (16). The excretions of all three electrolytes had risen by the seventh day, and the bottle fed babies excreted more of each of them than those having breast milk.

Discussion

These results are in keeping with what is known about the integration of food, growth and renal function in maintaining the stability of the internal environment in the first days of life. The production of surplus anions, particularly sulphates, in the newborn period is small owing to the metabolic balance being heavily weighted on the side of anabolism, and also because the requirements for growth are so perfectly met by the constituents and composition of breast milk. The results also show, however, that even the immature kidney of the newborn can materially increase its output of hydrogen ions if the infant is being fed on a cow's milk preparation. The large increase in the titratable acidity is made possible by the excess of phosphates in cow's milk. The excretion of titratable acid plus ammonia by these babies on a cow's milk preparation exceeded the corresponding figures for normal adults, and this suggests that the kidney at this age has functional reserve for the production and excretion of hydrogen ions if buffer substances are available. All the results and the comparisons with adults reported in this paper, however, have been expressed per kg of body weight, and this basis of comparison flatters the infant's functional capacity. On a basis of surface area the infants would have appeared much less capable, and the production of ammonia was never subjected to a severe test.

Gordon, McNamara & Benjamin (6) gave six infants aged 11, 15, 45, 51, 100 and 22 days ammonium chloride in divided doses for some days. The chloride was largely excreted and was accompanied to a major extent on the last day by an equiva-

lent amount of ammonium ions, but Gordon et al. concluded that the production of ammonia in some of the premature babies was subnormal. Fomon, Harris & Jensen (5) also investigated babies aged 2-6 months, some being reared on breast milk and some on cow's milk. They found that those being given cow's milk excreted much more phosphate and titratable acid, both before and after the administration of ammonium chloride. They also found that babies fed on cow's milk were excreting about four times as many ammonium ions as the others. Cort & McCance (3) found that the kidneys of puppies on the second day of their lives made a very poor response to single doses of acidifying drugs, and their results, although not obtained on the human infant, apply to the newborn period rather better than those of Gordon et al. and Fomon et al., for only two of their babies were less than 45 days old. Babies 7 days old are now being investigated by Hatemi (8).

Summary

1. Three tenths mEq of surplus anions not combined with fixed base were excreted by the kidney/kg of body weight/24 hours on the 1st day of life, 0.7 mEq/kg/24 hours on the 7th day by breast fed infants and 1.7 mEq by bottle fed infants. The figure for adults was 1.4 mEq/kg.
2. Before birth and for 2 days after birth very little phosphate was excreted. Consequently the titratable acidity was low and most of the surplus anions excreted by the kidney were present in the form of ammonium salts.
3. On the 7th day of life the amount of phosphate in the urine of breast fed in-

fants was still negligible and 82 % of the surplus anions excreted were in the form of ammonium salts.

4. Babies reared from birth on cow's milk excreted much more sulphate, but also more phosphate on the seventh day, which enabled them to excrete the additional hydrogen ions in the form of titratable acid. Only 42 % of the surplus anions were excreted in the form of ammonium salts.

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Studies of the Mechanics of Breathing in Children with Congenital Heart Lesions

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From the classical description of the mechanical dynamics involved in breathing by Rohrer in 1929, there is detailed information regarding the basic principles of respiratory movement of the thoracic cage. It is however, on the work of Christie & Meakins in 1934, who studied the interpleural pressure changes during breathing, that our knowledge about the actual forces required for ventilation of the lungs is founded. Through the work of Fry and coworkers in 1952 and Mead et al. in 1953, establishing the close resemblance under given conditions between the interpleural pressure changes and those registered in the esophagus, a practical technique for the appreciation of these forces was presented for clinical use. This technique allows the study of the mechanical properties of the lung, as a simultaneous recording of the esophageal pressure changes and the associated ventilated volume and air-flow-rate is capable of giving information regarding the readiness with which the lung parenchyma is aerated. The forces required for the ventilation of the lung are governed mainly by two different components: the friction of the air flow in the bronchial tree and the elastic recoil of the lung parenchyma

itself. The latter of these two components can readily be isolated by measuring the intraesophageal pressure difference between two lung volumes when no airflow is present, i.e. end expiration and end inspiration, and is expressed in $1/\text{cm H}_2\text{O}$, or for greater convenience in children in $\text{ml}/\text{cmH}_2\text{O}$. This ratio then denotes the distensibility of the lung parenchyma and has been termed "compliance". The greater the volume changes per unit pressure, the less resistant is the lung to distension and the higher is its compliance, and vice versa.

Since this method of analysing the mechanical properties of the lung was introduced, our knowledge in this field has been enriched considerably. Lung compliance in normal adults has been determined and the rather wide normal range for this value pointed out (5, 21). It has also been found that the compliance of the lung is fairly well correlated with other parameters of the lung such as vital capacity and functional residual capacity (4, 7, 13, 23, 26). In addition pathological conditions have been studied by this technique, and reports regarding changes in the mechanical properties of the lung in various cardiac conditions are particularly numerous.

Already in 1891, it was suggested by von Basch that vascular congestion in the lungs might cause a stiffening of the parenchyma and this hypothesis has indeed been found to be true. Various authors, all studying mainly rheumatic valvular lesions (4, 6, 9, 18, 27, 29) have reported a decreased compliance in patients with lung congestion and very low values have been observed in pulmonary edema (9, 27). These findings have been experimentally verified both in man and animals. Bondurant et al. in 1957 induced acute vascular congestion in the lungs of normal men and could record an immediate decrease in lung compliance, which returned to normal when the congestion was relieved. Similar experiments have been performed by others in animals (14, 17) leading to the same conclusion. It is evident from the foregoing that pulmonary vascular congestion has a marked influence upon the distensibility of the adult lung, seemingly related to the degree of congestion. The large variety of congenital heart lesions seen in a pediatric clinic, often with drastic changes in flow and pressure in the pulmonary vascular bed, although rarely leading to congestion, has warranted more information regarding the effect of these changes upon the mechanical properties of the lung. In infants and small children, however, the method of studying pulmonary compliance is not as easily applicable, as it requires the cooperation of the patient to record quiet breathing after the introduction of the esophageal catheter. It is therefore not surprising that apart from information obtained while studying the newborn infant (8, 15, 16, 20) our present knowledge about the mechanical properties of the

lungs in small children is very limited. It is the purpose of the present article to report a study of the effect of altered circulatory conditions due to various cardiac malformations upon the mechanical behaviour of the lungs in young children. An attempt is also made to correlate the findings to the changes in the various hemodynamic and clinical parameters.

Material and Methods

Twentyfive children, ranging in age from 24 hours to 15 years, with various congenital heart lesions, were studied previous to right heart catheterization. Pertinent data regarding this group of children, including results of the catheterization, are listed in Table 1. Children less than 8 years of age were routinely premedicated with 0.03 mg Bellafolin Sandoz per kg for body weights less than 15 kg and with 0.02 mg morphine-scopolamine per kg for those over 15 kg. An additional dose of 15–25 mg of an antihistamine was given to children more than one year old. This premedication usually sedates the child enough to facilitate the introduction of the esophageal catheter. Their reflex response pattern is however intact, and they react immediately to painful stimuli. The only noticeable effect upon the respiration of this medication that was observed, was that it became more regular. It was repeatedly demonstrated in children more than 7 years old, that were studied both with and without this premedication, that no systematic change in the calculated compliance could be attributed to the medication.

Eleven normal infants and twenty older children, that were being considered to be healthy from a cardio-respiratory point of view, and were admitted to the hospital for minor surgery, served as a control group. The older children, preoperatively premedicated in the same way as the cardiac group, were studied prior to surgery. Of the thirty "healthy" children, 11 were from four days to four weeks old, 6 were from two months to

two years old, 8 from two to eight years old and the remaining five children from eight to fifteen years old. All children were studied in the recumbent left lateral position in order to minimize the effect of the impression of the heart upon the esophagus. Although the supine position is not ideally suited for esophageal pressure measurements, there was in the present series no means of studying the patients in any other position. The technique used for measuring the compliance was that described by Karlberg (16). A polyethylene catheter with an internal diameter of approximately 1 mm and filled with water was introduced through the mouth and placed with its multiperforated tip in the upper half of the esophagus. Pressure differences occurring were recorded via a strain gauge manometer (Elema) on a four channel direct writing recorder. Care was taken to secure a position of the catheter where the impact of the heart beats was at a minimum. The catheter was flushed at regular intervals to obtain good passage. At the end of each tracing the catheter was slowly extracted while recording. It was found in this way, that not until the catheter was about to leave the thoracic esophagus was there any systematic change in the recorded pressures. Simultaneously with the esophageal tracing, the tidal volume was recorded by allowing the child to breathe into a closed system with a volume of 60 litres for children less than 6 months old and 300 litres for older children. The pressure differences produced in this way were recorded via a strain gauge manometer and fed to another channel of the recorder. They were then interpreted as volume changes against calibration with a known volume. The volume of the system was chosen so as to be large enough to avoid resistance to respiration, and it was calculated that the pressure variations occurring in the system did not exceed cmH_2O . In order to reduce rebreathing during the registration, a pump with a 4 litre per minute capacity kept the air circulating. For the calculation of compliance, care was taken to obtain a series of at least 10 consecutive breaths, that were without signs

of interference from esophageal contractions, and where the end-expiratory level was kept at approximately the same level. The mean value of the eight middle breaths was taken as representing the compliance of the lungs and was expressed in $\text{ml/cmH}_2\text{O}$.

Results

The compliance values for the normal group are plotted as circles in Fig. 1 on a double logarithmic scale against the body length. The regression line for this group, calculated according to Snedecor (28), is drawn as a solid line, together with the 95 per cent confidence limits. It is noteworthy that the slope of the regression line is almost identical with that constructed by others (13) for older children, and that, although the techniques used have been somewhat different, there is virtually no distance between the two lines. The cardiac cases are listed in Table 1 together with values from the catheterization. The compliance values for this group are also plotted on Fig. 1 as solid circles. The regression line for this material is marked as a dotted line. Co-variance analysis of the two lines shows, that the cardiac group has a significantly lower compliance ($p < 0.01$) than the normal group. There is no significant difference between the slopes of the two lines ($p > 0.1$). The distribution of the individual observations indicates that the relative reduction in compliance varies considerably from case to case. In order to determine if there exists any correlation between the reduction in compliance and the various hemodynamic parameters, the compliance, expressed as per cent of the normal mean value, was plotted against pulmonary artery pressure, Fig. 2, left atrial or wedge pressure (PCV), Fig. 3 and

TABLE 1.

Pertinent data regarding the cardiac group. The following diagnostic abbreviations are used: A.S.D. = atrial septal defect, V.S.D. = ventricular septal defect, P.D.A. = patent ductus arteriosus, P.S. = infundibular or valvular pulmonary stenosis, M.S. = mitral stenosis, A.V.R. = anomalous venous return. All pressures are expressed in mm

Case	Sex	Age	Weight kg	Height cm	Resp. rate	Compliance ml/cm H ₂ O	Compliance in % of normal mean	P.A. syst. pressure	L.A.- P.C.V. pressure	Flow Pulm: system.	Diagnosis
1	M	24 h.	2.9	49	70	2.0	43	80	—	—	Prim. pulm. hy-
2	M	1 m	4.6	58	70	2.7	36	60	—	—	tension
3	M	2.5 m	3.0	48	68	3.9	87	60	6	—	Corrected transp.
4	F	3 m	3.9	53	65	3.6	62	19	5	—	Tricusp. atresia
5	M	4 m	5.4	65	90	2.2	22	83	—	1.5	V.S.D. + P.S.
6	F	5 m	3.2	56	45	6.9	100	95	—	—	V.S.D.
7	F	5 m	5.8	61	33	7.1	83	—	12	1.8	Transposition
8	F	5 m	5.6	64	50	7.8	80	35	10	2.4	V.S.D. + P.S.
9	M	5 m	4.8	62	75	2.6	29	40	17	—	V.S.D.
10	F	7 m	7.3	67	42	6.8	62	43	1.5	2.1	M.S.
11	M	8 m	5.2	63	36	1.6	17	75	5	—	V.S.D.
12	F	8 m	6.6	66	70	7.5	71	94	—	1.2	Corrected transp.
13	M	9 m	5.8	69	48	7.5	62	51	13	1.4	P.D.A.
14	M	18 m	10.9	83	50	3.7	18	47	27	—	A.V.R.
15	F	2 y	9.1	82	60	7.0	36	70	—	3.3	Corrected transp.
16	M	2½ y	11.1	82	30	8.7	44	11	8.5	—	P.D.A.
17	M	4 y	17	105	24	21	55	20	—	—	Tricusp. atresia- pulm.atresia
18	M	4 y	12.9	97	40	33	110	44	—	1.2	P.S.
19	M	4½ y	16.2	107	40	10	25	72	9	1.3	V.S.D.
20	F	9½ y	41	142	35	30	33	17	—	—	P.S.
21	F	9½ y	29	138	17	35	47	25	—	3.0	A.S.D.
22	M	11 y	26.7	139	21	38	44	14	—	—	Fallot
23	F	11½ y	33	144	18	60	66	55	7	1.3	A.S.D.
24	M	15 y	46	164	27	62	48	14	6	—	P.S.
25	F	15 y	25	135	15	46	60	28	—	2.4	A.S.D. + P.S.

against the amount of left to right shunt expressed as the ratio of flow in the lesser circulation to that of the systemic, Fig. 4. Statistical analysis of these three relationships failed to show any significant correlation.

Greatly reduced compliance values were not associated with any specific cardiac diagnose.

Discussion

The relationship of pressure alterations in the pulmonary circulation to the change in the elastic properties of the lungs has been studied in adults by several investi-

gators. Pryor et al. in 1955 studying mitral stenosis by heart catheterization concluded that the PCV pressure, reflecting the left atrial pressure, did not have to be elevated in cases with decreased compliance, but that hypertension in the pulmonary artery was accompanied by a reduced compliance. These authors also reported high norm alvalues in cases with pulmonary hypotension. Saxton et al. (26), however, found no significant correlation between pulmonary artery pressure and the reduction in compliance usually found in congestive heart failure. The authors stress the positive correlation between vi-

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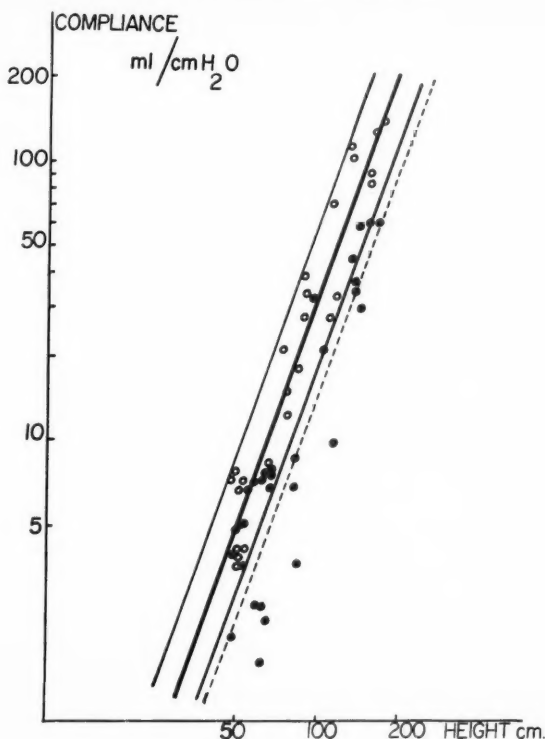


Fig. 1. The relationship between the compliance calculated for the "healthy" children (circles) and the cardiac cases (solids) and body length in cm. Compliance is expressed in ml/cmH₂O. The solid lines represent the regression line and the 95 per cent confidence limits for the normal group. The dotted line is the regression line calculated for the cardiac group. Regression line equations: Normals: Compliance = $ht^{2.7381} \cdot 1.104 \cdot 10^{-5}$. Cardiacs: Compliance = $ht^{2.6316} \cdot 8.486 \cdot 10^{-5}$. The distance between the two lines is significant ($P < 0.01$).

tal capacity and compliance even in these pathological cases, and discuss the causal relationships between these two parameters. Lately McIlroy et al. (19), have published a series of patients with hypertension in the pulmonary circulation due to various heart lesions. They conclude that the pressure per se does not seem to play an important role in the reduced compliance found in most of their cases, but rather that parenchymal changes se-

condary to the hypertension are implicated.

It is evident from the above studies that, although a tendency to reduction in compliance is found in many cardiac cases, the opinions regarding the explanation for this reduction are still numerous and in many respects conflicting.

The finding that the calculated compliance in the present material of cardiac

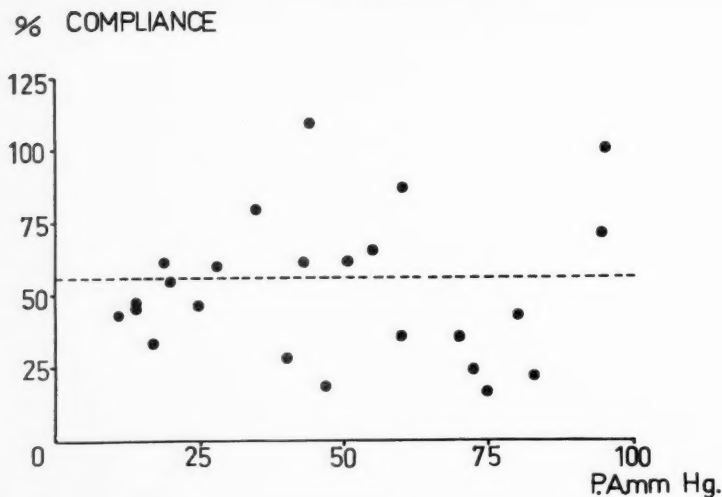


Fig. 2. The relationship between systolic pulmonary artery pressure and compliance, expressed in per cent of the normal mean for corresponding height. No significant correlation was found. The dotted line represents the lower limit of the 95 per cent confidence interval.

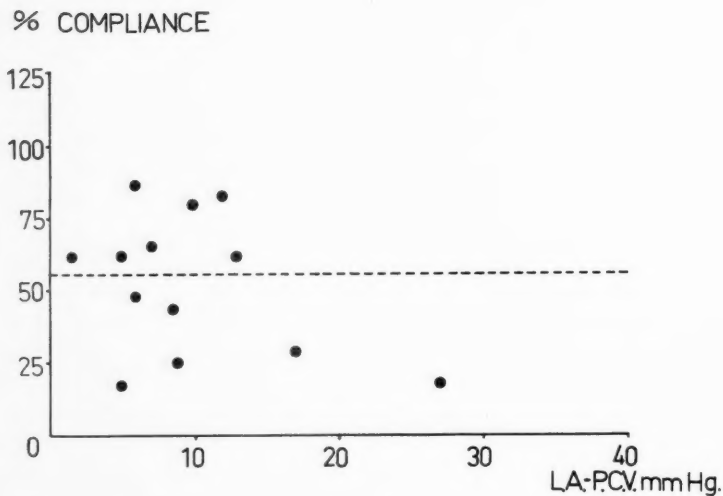


Fig. 3. The relationship between left atrial or pulmonary wedge pressure and compliance, expressed in per cent of the normal mean for the corresponding height. No significant correlation was found. The dotted line represents the lower limit of the 95 per cent confidence interval.

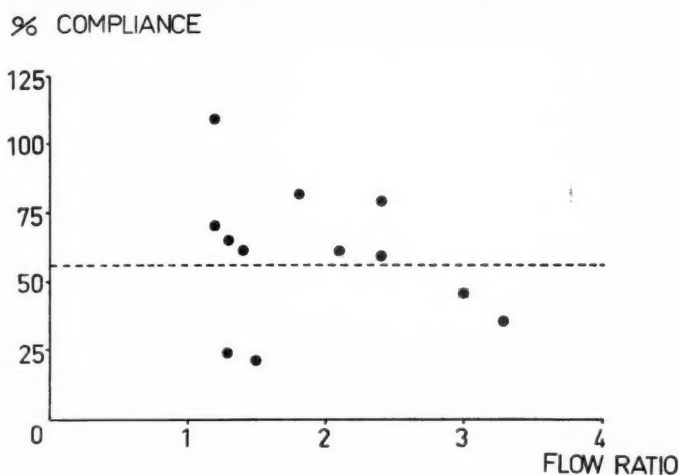


Fig. 4. The relationship between pulmonary flow, expressed as the ratio pulmonary/systemic flow, and compliance, expressed in per cent of the normal mean for the corresponding height. No significant correlation was found. The dotted line represents the lower limit of the 95 per cent confidence interval.

cases is significantly lower than the values obtained for the normal group, raises some questions of great importance. First of all, it is essential to know whether the esophageal pressure recordings in the cardiac group really reflect the true pressure gradient over the lung. It has to be born in mind, that altered anatomical conditions, as introduced for instance by the cardiomegaly present in most of the pathological cases, might conceivably interfere with the transmission of the transpulmonary pressure to the esophagus. It has also recently been questioned (3) whether pulmonary congestion per se might not render the esophageal pressures unreliable. As pulmonary congestion was a rare finding in the present material, indeed only pronounced in one of the cases, this condition could not have greatly influenced the obtained values. The finding that the pressures recorded from different levels in the upper half of the esophagus

did not show any discernable difference, is taken to indicate, that the influence of the cardiac impression upon the esophagus may be considered negligible. The impact of the often forceful heart beats in the cardiac group, may render the pressures recorded from the esophagus less precise than in the normal material. The coefficient of variance of the eight determinations in each case has been calculated, and the mean value for this co-efficient, was in both groups found to be of the same order ($\pm 11.6\%$ in the cardiac group and $\pm 10.3\%$ in the control group), indicating that the recorded pressures are no less representative in spite of the altered activity of the heart in the cardiac group.

The moderate increase in respiratory rate found in the cardiac patients may interfere with the calculated compliance value, due to an increased time-lag between the intraesophageal pressure changes and the recorded volume changes during

rapid breathing. Our experience with compliance determination in the cardiac patients is, however, that an increase in respiratory rate of about 20 to 25 per cent in the same tracing, usually is not capable of producing significant changes in the calculated values. As an increase of this size over the respiratory rate in the normal group was not consistently accompanied by low compliance, we are led to believe that the observed tachypnoea per se is not responsible for the reduced compliance in the present series.

If it is accepted, that the present result really denotes a true reduction in compliance in the cardiac group, what then may be the causative factor for this reduction. There are principally two different ways of reducing the compliance, namely a qualitative change in the lung tissue, i.e. fibrosis, or a quantitative change, interfering in a negative way with the ratio aereated/non-aereated lung tissue. Conceivably a combination of both these factors may be responsible.

Pulmonary vascular hypertension per se, as well as vascular changes secondary to hypertension might in the present material well be thought of as being responsible for a qualitative change, or a "stiffening" of the lung parenchyma. Were the hypertension itself the causative agent, a correlation would be expected between the pressure in the pulmonary artery and the reduction in compliance. In agreement with similar studies in adults (19, 20), this is not the case in the present material. As the pulmonary hypertension, particularly early in the disease may be caused by a combination of functional and organic vascular changes, the latter are not necessarily well correlated with the degree of

pulmonary hypertension. The mere fact, however, that in cases with hypotension in the pulmonary artery a reduction in compliance may be recorded, makes secondary hypertensive changes as the main cause very unlikely.

As qualitative changes of the parenchyma, directly related to hemodynamic changes, do not seem to play an immediate role in the reduction of the compliance, the possibility of a quantitative change, leading to a reduction of the ratio aereated/non-aereated parenchyma, must be considered. This may be brought about as a direct consequence of an increased pulmonary blood volume, as suggested by Hamilton (11) and Mills (22), and it has indeed been shown experimentally in the dog, that there is a positive correlation between the amount of blood stored in the lung and the reduction in compliance (12). Such an increase in the pulmonary blood volume might be caused by an increased pressure on the post-capillary side of the lung, or merely by an increased flow through the lung. Both of these factors, however, would have to be great enough to produce a pulmonary vascular dilatation. Saxton et al (26), studying patients with mitral stenosis before and after surgery, were unable to find a correlation between pulmonary blood flow and compliance, and Borst et al (3) showed experimentally in the dog, that even very marked increase in the pulmonary flow, does not seem to change the compliance, until there is a pronounced increase in post-capillary pressure and signs of heart failure with pulmonary congestion are imminent. It is evident from these studies that flow and pressure in the lungs can vary surprisingly much without inter-

ence with the mechanical properties of the parenchyma, and that there exists something like a threshold that has to be reached before the pooling of blood in the lungs may interfere with the compliance. It is thus not surprising that the admittedly few observations on flow and postcapillary pressure in the present material did not correlate significantly with the reduction in compliance. It may be assumed that even if these parameters do play a role in cases with excessive flow or congestion of the lungs, there is little reason to implicate an interference with the mechanical properties of the lungs in the present series of cardiac cases.

A space occupying factor, that may markedly interfere with the ratio aereated/non-aereated parenchyma, is presented by the heart itself. The often pronounced cardiomegaly seen in children with various congenital heart lesions may thus quite feasibly interfere with the compliance of the lungs. Among the observations made from the radiographic studies of the present material, the heart volume can be estimated with accuracy, and preliminary studies, although incomplete, suggest a more than coincidental relationship between relative heart volume and reduction in compliance. Also the well known phenomenon that a lowering of the diaphragm is often seen associated with a big heart in children, may conceivably reflect an altered mechanical behaviour of the lungs in these children, as a compensatory response to a reduction in the aereated volume.

Further studies of the relationship between radiographic findings and alterations in the mechanical properties of the

lungs in children with congenital heart lesions are being carried out, and will be reported in a forthcoming communication.

Summary and Conclusions

Twenty-five children, one day to fifteen years old, with various congenital cardiac conditions, were investigated with respect to their pulmonary compliance, previous to heart catheterization. It was found, that the premedication routinely given to these children before catheterization, sedated them enough to facilitate the investigation even in children less than 7 years of age, without signs of interfering with the determined values of lung compliance. Normal newborns and children admitted to the hospital for minor surgery served as a control group, and were studied under identical conditions as the cardiac group.

The cardiac group had a significantly lower compliance than the control group. In agreement with the findings in older children and adults, no correlation was found between the reduction in compliance and the pressures in the pulmonary artery, the left atrium or in the pulmonary capillary wedge; nor with the amount of flow in the pulmonary vascular bed.

The authors conclude, that rather than being directly due to hemodynamic alterations in the lungs, this reduction in compliance is probably due to a decreased lung capacity. X-ray studies suggest that the space occupying influence of the enlarged heart may have a significant influence upon the compliance of the lungs in these children. Further studies as regards this relationship are being carried out.

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CASE REPORT

Severe Anemia in a Newborn Caused by Protracted Feto-Maternal "Transfusion"

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In 1948 Wiener (14) suggested the possibility of hemorrhagic shock in the newborn produced by transplacental hemorrhage from the fetus into the mother's circulation. Wickster's (13) findings in 1952 supported this theory. Chown (1, 2) proved by serological technique and biochemical analyses that feto-maternal "transfusion" could result in severe non-hemolytic anemia in the fetus. In one of his cases there was a probable transfusion reaction observed in the mother.

Other investigators have since confirmed Chown's findings (4, 5, 6, 10, 11). Some of them suppose the occurrence of transplacental bleeding to be much more common than the few reports would indicate. O'Connor *et al.* (9) examined 17 mothers whose babies were pale and anemic and found higher values of fetal hemoglobin in their blood than in the controls. These infants showed symptoms varying from just pallor to severe hemorrhagic shock. It is therefore possible that the hemorrhage may in many instances be of only a moderate degree, the infants having only a slight anemia which may easily be overlooked.

Below is reported a case of severe anemia in a newborn. The condition was assumed to be due to blood loss which by serological investigations was proved to be caused by feto-maternal hemorrhage.

Case Report

The mother was a 24 years old primigravida. She had been to routine controls during the pregnancy without any abnormalities being noted. The baby was born 17 days before term. Labor lasted for 11 hours, the fetal sounds were normal (120/min). The delivery was uneventful, the total bleeding calculated to 50 ml. Placenta appeared grossly normal, weight 600 g (unfortunately not saved for further examination).

The infant, a boy, measured 51 cm, the weight was 3700 g. At birth he was extremely pale with weak cry and gasping respiration. Hemoglobin taken shortly after birth was less than 3.7 g/100 ml. He was given oxygen and immediately transferred to the Pediatric Department.

On admission, 1½ hours old, he was in a very poor condition. The most striking signs were extreme pallor and generalized edema. The respiration was irregular, slow and grunting. There was no visible cyanosis or icterus, and no skin hemorrhages. Moro's reflex could not be elicited. The anterior

fontanel showed normal tension. In contrast to the pallor and anemia, the heart action was slow (80/min) and forceful. There were no heart murmurs. The abdomen appeared distended and there seemed to be edema of the abdominal wall, but no clear signs of ascites. Spleen and liver were not palpable.

Preparations were made for immediate transfusion with O Rh—blood through the umbilical vein. When the cord was cut, blood gushed violently from the vein and the venous pressure was measured to more than 15 cm. Instead of giving a simple transfusion it was therefore decided to do an exchange transfusion which was done at 10 ml increments, 455 ml out, 425 ml in. At the end of this the venous pressure was 12 cm and hemoglobin 6 g/100 ml. The exchange transfusion was continued with concentrated red cell suspension, 150 ml in, 150 ml out (plus some bleeding around the catheter). After this the venous pressure was 6–8 cm and the hemoglobin 12.2 g/100 ml. The patient was continuously given oxygen. During the transfusions he became gradually cyanotic. The respiratory distress seemed unchanged. In the course of the following hours the edema and the cyanosis gradually disappeared. Twelve hours old he had an almost normal colour, there was no respiratory distress. He was still weak but had an almost normal Moro's reflex, a good grasp and a good sucking reflex. The heart action was regular, 120/min. Auscultation of the lungs revealed good respiratory sounds, but with scattered crepitant rales. However, there was a fall of the hemoglobin to 9.15 g/100 ml.

During the following 12 hours his condition deteriorated. The edema reappeared, and he became deeply cyanotic in spite of oxygen therapy. The respiratory movements became gradually shallow and slow and the heart action slow, weak and irregular. He died 26 hours old.

Autopsy: Heart: no pathological findings. Lungs: poorly aerated fetal lungs. Several

areas of massive intraalveolar hemorrhages. In other areas typical hyaline membranes. Some bronchopneumonic foci. Liver: weight 140 g. The usual picture of extramedullary hematopoiesis. Spleen: weight 7 g. Brain: weight 350 g. The brain substance of very soft consistency. No visible hemorrhages on the surface or in the ventricles.

Laboratory findings: Cord blood before transfusion: hemoglobin 2.8 g/100 ml, Rbc. 840,000/cmm. Nucleated blood corpuscles 61,000/cmm whereof about $\frac{2}{3}$ nucleated red cells. Serum bilirubin (total) 0.75 mg/100 ml. Total serum proteins 3.3 g/100 ml. Aspirated bone marrow from the tibia showed intense erythropoiesis with a great number of mitoses. The leukopoiesis appeared normal. Megacaryocytes were present.

Serological Findings

Mother and child were both O Rh+. Cord blood showed a negative direct antiglobulin test. The indirect antiglobulin reaction between the mother's serum and the infant's cells was also negative.

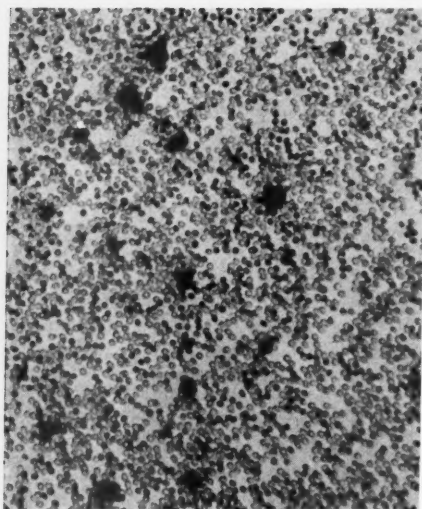
It was neither possible to demonstrate antibodies in the mother's serum against the infant's cells nor against a panel of 9 standard cells (saline technique at 18 and 37°C, albumin and antiglobulin techniques at 37°C). The mother's serum showed no reaction with papainized O₁R₂ cells at 37°C.

A more extensive grouping of mother and child revealed (see down).

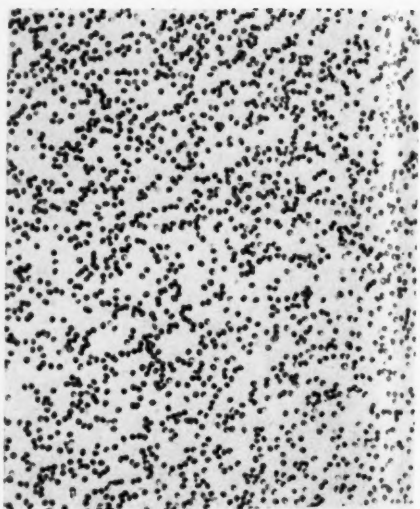
When red cells from the maternal circulation were tested against saline agglutinating anti-N and anti-c sera, a distinct partial agglutination was noticed indicating the presence of a minority of N+c+ cells (Fig. 1). It was reasonable to assume that these cells represented red cells from the child which had entered the mother's circulation.

In order to calculate the number of these cells in the maternal blood, M+N+c+ and M+N-c-c- cells (from blood donors) were mixed in known proportions and the mixtures

Mother:	O	M+	N- ⁺	S+	P+	C+	C ^W -	D+	E-	c- ⁺	K-	Fy(a+)	Jk(a+b-)
Child:	O	M+	N+	S+	P+	C+	C ^W -	D+	E-	c+	K-	Fy(a+)	Jk(a+b-)



A.



B.

Fig. 1. A: Cells from the mother's circulation taken at the day of delivery and tested with anti-N. A distinct partial agglutination is seen, demonstrating a minority of N+ cells. B: Cells from N- blood donor tested with the same serum.

tested with the same sera as used in the grouping of the mother and child. Partial agglutination of the same degree as that observed in the mother's blood was apparent when the ratio of M+N+c+ to M+N-c- cells was approximately 1:20.

Seven days post partum partial agglutination with anti-N was present to a lesser degree but no longer demonstrable with anti-c. No antibodies were found when the serum was tested against the same panel of standard cells and under the same conditions as mentioned above. Fourteen days post partum no N+ cells could be demonstrated in the mother's circulation. Neither anti-N nor anti-c had appeared in the mother's blood when tested 1 month after delivery.

Discussion

Clinically our case presented symptoms similar to those of hemolytic disease of the newborn with hydrops. However, the serum bilirubin was normal and the sero-

logical investigations showed no evidence of hemolytic disease. The bone marrow and the peripheral blood showed a marked regeneration which excluded the diagnosis of a possible hypoplastic anemia. We were therefore convinced that the anemia was caused by hemorrhage. As there was no vaginal bleeding during the pregnancy and as the blood loss during delivery, even if the greater part of it should originate from the child, was too scanty to explain the severe anemia of the infant, a feto-maternal "transfusion", as demonstrated by the serological investigations, most probably had caused the symptoms.

Most of the previously reported cases of transplacental hemorrhage have presented symptoms of shock; pallor, tachycardia and subnormal venous pressure. In some of them the hemoglobin was normal at birth but decreased rapidly during the

first hours of life. Most of them have been successfully treated with simple blood transfusions. The bleeding has been considered to have taken place shortly before or during delivery. However, Weiner *et al.* (11) were able to demonstrate a considerable amount of fetal blood in a mother's circulation several weeks before term. She gave birth to a child with severe anemia but also with symptoms of hemolytic disease.

Our case did not present the usual symptoms of acute hemorrhagic shock produced by bleeding at the time of delivery. The severe non-hemolytic anemia at birth with marked erythroblastosis, the elevated venous pressure, the slow and forceful heart action, the low serum-proteins and the generalized edema are taken as valuable evidence that the hemorrhage, similar to that in the case reported by Weiner *et al.*, has started during the latest weeks of the pregnancy and probably persisted until delivery.

We do not think it possible to estimate the exact quantity "transfused" in this case. Only a rough calculation may be done on the basis of the infants blood values and of the partial agglutination in the mother's blood. We presume that the infant was deprived of more than $\frac{3}{4}$ of its blood, probably 250-300 ml, during the latest period of its intrauterine life.

The marked reduction of red cells in the infant's blood in spite of the intensive regenerative reaction also indicates the severity of the hemorrhage.

It is astonishing that the fetus could survive such a blood loss, resulting in the exceptionally low values of hemoglobin (< 3.7 g/100 ml) and red cells (0.84 mill/cm³) at birth. The possible explanation

might be that the bleeding has been slow and even so that the fetus has had time to compensate for the blood loss mainly by increasing the plasma volume and, to some extent, by forced regeneration.

As the mother did not have any antibodies against the child's red cells it was not to be expected that the fetomaternal hemorrhage would cause any "transfusion" reaction in the mother. We do not find it extraordinary that no irregular antibodies could be demonstrated in the mothers serum 4 weeks after delivery as the actual antigens (N and c) generally are accepted as weak ones.

The elevated umbilical venous pressure is a clear sign of cardiac failure. As several investigators (8, 12) have stressed in connection with severe hemolytic anemia of the newborn, the anemia will cause myocardial hypoxia which in turn gives cardiac failure. The heart failure has been considered the major cause of the edemas in these cases. In our case the marked hypoproteinemia may as well have been the dominating factor. Most probably the infant also had cerebral edema which in addition to the hypoxia of the central nervous system might have been responsible for the bradycardia.

It is previously shown (3, 7) that infants suffering from acute hemorrhagic shock caused by fetal bleeding at the time of delivery should be given simple blood transfusion. In cases like ours presenting symptoms of severe anemia and cardiac failure, simple blood transfusion will give an undesired increase of the blood volume and is therefore contraindicated.

The preferable treatment is immediate exchange transfusion with whole blood or concentrated red cell suspension. During

this procedure one must gradually reduce the venous pressure by withdrawing a larger volume than the one injected. The exchange transfusion should be carried out until signs of anemia and heart failure have disappeared.

This therapy was not sufficient to save the life of our patient. The clinical symptoms and the findings at autopsy indicate that the longlasting anemia had produced irreversible changes. The infant was probably beyond any therapy at the time of birth.

Summary

A case of severe anemia in a newborn is reported. The anemia was caused by a fetomaternal "transfusion". Fetal red

cells could be demonstrated in the mother's circulation by serological technique. The infant did not present the usual signs of shock caused by a sudden hemorrhage at the time of delivery. The clinical signs were similar to those of hemolytic disease of the newborn with hydrops, but a hemolytic mechanism as a cause of the anemia was excluded. The clinical condition and the laboratory findings indicated that the blood-loss probably had started during the latest weeks of the pregnancy and persisted until delivery.

As the infant presented signs of cardiac failure, simple blood transfusion was contraindicated and exchange transfusions were given.

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CASE REPORT

Heinz Body Anaemia with Splenic Hypoplasia

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In 1952 Gasser & Willi described a complex of congenital malformations characterized by situs inversus, asplenia and a severe form of cyanotic congenital heart disease which could be diagnosed by finding Heinz cell bodies in the blood. Similar cases have since been reported by Polhemus & Schafer (1955), Nihoyannopoulos *et al.* (1956), Aguilar *et al.* (1956), Plowman (1957) and Levy (1957). All these cases had multiple congenital abnormalities and Heinz bodies were found in the peripheral blood but there was nothing to suggest that the Heinz bodies were causing a haemolytic anaemia.

We have recently encountered a case which has certain features of this syndrome but which, in addition, had steatorrhoea and a haemolytic anaemia associated with the appearance of Heinz bodies similar to those described by Varadi (1957), Allison (1957) and others.

Case Report

D.C. was admitted to the Hospital for Sick Children on 12.5.57 aged nine weeks.

His birth-weight was 2250 g, having been born six weeks prematurely by Caesarian section. He was one of twins, the other dying in utero. For the first week of life penicillin

had been administered prophylactically. He was not given any Vitamin K and was not jaundiced at birth. The mother's blood was Rhesus negative and the father's Rhesus positive. This baby was Group "O" Rhesus positive. There had been three previous normal pregnancies and no antibodies had been detected in the mother's blood during this pregnancy. Initially he fed with some difficulty but was discharged from the Maternity Home at five weeks, weighing 2520 g. At home he was noticed to be passing large, loose, pale, offensive stools and his abdomen was constantly distended. Over the next three weeks there was no weight gain and the child had intermittent attacks of vomiting. Despite alterations in feeding, he vomited persistently and one week later he was transferred to the Hospital for Sick Children for further investigation.

On examination he was very underweight, looked markedly anaemic and mildly jaundiced. There was generalized abdominal distension but no evidence of ascites. There were no palpable masses and liver, spleen and kidneys could not be felt. There was no visible gastric or intestinal peristalsis and bowel sounds were normal. Cyanosis was not apparent and the lungs and the cardiovascular system were clinically normal. There were no further abnormalities to be detected on clinical examination. The urine was dark brown in colour and the stools were pale and clinically resembled the stools of steatorrhoea.

The following investigations were performed:

Blood Examination

R.B.C. 1.4 million/cu.mm. Hb. 5.3 g%.
 Reticulocytes 32%. The R.B.C. are large and polychromatic. No spherocytes seen. Fragility: Haemolysis commenced at 0.5 g% NaCl and was completed at 0.3 g%.
 W.B.C. 16,300/cu.mm (N. 39%, L. 61%)
 Film: There are 40 normoblasts per 100 W.B.C.

Platelets 392,000/cu.mm.

Blood group "O" Rhesus positive

Direct Coombs' test negative

Blood culture negative

Urine—Urobilin positive + +. Bilirubin trace.

Stool—Stercobilinogen positive + +. Gelatin digested at a dilution of the faeces of 1:400. Total fat 60 g per 100 g of dried faeces (24 hr collection).

Bone marrow—granulocytes 68%
 lymphocytes 18%
 erythroblasts 14%.

(The granulocytes showed a marked shift to the left and the normoblasts were poorly haemoglobinised.)

Serum bilirubin 2.1 mg per 100 ml

Alkaline phosphatase 18 units

Thymol turbidity less than 1 unit

Kunkel less than 1 unit

Total serum protein 3.9 g

Electrophoresis — gamma globulin increased

Prothrombin concentration — normal.

Serum electrolytes — Na 134 mEq/l

K 3.9 mEq/l

HCO₃ 23.1 mEq/l

Cl 103 mEq/l

X-rays: Chest—cardiac outline normal.

Abdomen—obvious abdominal distension. No fluid levels or other abnormality noted.

This infant appeared to have a haemolytic anaemia and required urgent transfusion. He was given 150 cc of packed cells which raised his haemoglobin to 12.5 g and following this the haemolysis ceased, the jaundice

waned and the urine contained less urobilinogen. During the next week the haemoglobin remained in the region of 12 g with 10–15% reticulocytes in the peripheral blood. Ten days after admission the child had a further but less severe haemolytic episode. The haemoglobin fell to 9 g and he again became jaundiced, his abdominal distension was gross and he began to vomit. Again he was transfused with 100 cc packed cells and maintained on intravenous fluids for 24 hours. At this stage it was first noticed that 50% of the red cells contained Heinz body inclusions. The day following the transfusion 80% of the red blood cells contained Heinz bodies. From this it seemed probable that Heinz bodies were appearing in the transfused red blood cells but no toxic factor could be incriminated to account for them. The haemoglobin rose to 14 g after transfusion but fell to 10 g over the next two days. The haemolysis again ceased after 48 hours.

Over the next week the Heinz body count progressively fell until none were observed after nine days. During these bouts of acute haemolysis the child's spleen was never palpable. This was thought to be an unusual feature and the possibility of congenital absence of the spleen was considered, in view of its known association with the appearance of Heinz bodies in the peripheral blood. The abdominal distension and vomiting persisted and the child continued to pass loose, pale stools. The likelihood of a partial or intermittent intestinal obstruction became more obvious. A barium meal showed large coils of dilated small bowel but no actual obstruction. On the 6.6.57 his distension and vomiting became worse, visible peristalsis became apparent and he appeared to be acutely obstructed. A straight X-ray of the abdomen showed multiple fluid levels.

A laparotomy was performed by Mr. Waterston. A volvulus at the lower end of the ileum was found, the bowel proximal to this being grossly dilated. The volvulus had occurred around a stenosed segment of gut about 7.6 cm. A band was seen to run from the proximal end of this stenosed segment of ileum to the umbilicus. The whole of the

gut was in fact present on a universal mesentery and the caecum was undescended. The liver was centrally placed. A very tiny spleen was found high up under the left diaphragm, which was thought to be about a quarter of the normal size for an infant of his age. A resection of the stenosed gut and an end-to-end anastomosis was performed. The immediate postoperative progress was fair.

There were no further haemolytic episodes. The child developed generalised oedema coincident with a marked drop in his serum proteins to 2.9 g/100 ml. This was corrected with an infusion of sodium-free albumin. Vomiting continued on and off, and his distension returned.

In a further ten days he had developed visible peristalsis and was obviously obstructed again. Conservative measures having failed, then despite his poor general condition, a further laparotomy was embarked upon.

The anastomosis site was bound down with adhesions and a large abscess cavity had formed in this region. This was freed and a double-barrelled ileostomy was performed. Despite this he survived only five days after this second operation. Permission was not given for post-mortem.

Discussion

Heinz Bodies

The presence of inclusions within the erythrocyte which stain with supra-vital dyes such as methyl violet, were first recognised by Reiss (1882), and were described more fully by Heinz (1890). They are found in a variety of toxic conditions, particularly in naphthalene poisoning (Zuelzer & Apt 1949) following an overdose of sulphapyridine (Stats *et al.* 1948) and were sometimes found when polycythaemia used to be treated with phenylhydrazine (Dacie 1954). They have also been noted in patients who have under-

gone splenectomy. It is assumed that the formation of Heinz bodies occurs when the cell membrane is damaged, the erythrocyte becomes distorted in shape and is earmarked for premature destruction.

Allison (1957) suggests that Heinz body anaemias occurring in infancy may follow two patterns. The first is found only in premature infants, and is not associated with other congenital anomalies, it may be of varying severity but the prognosis is usually good. In the second type the baby is born at full-term, there are other congenital abnormalities and frequently the baby does not recover.

The majority of cases of haemolytic anaemia associated with the presence of Heinz bodies have occurred in premature infants. Gasser & Carrer (1948) drew attention to this fact when they reported the case of a baby weighing 1530 g at birth who had a normal peripheral blood count at the outset but subsequently became jaundiced and was noted to have Heinz bodies in half its R.B.C.'s. Despite blood transfusions he died at the age of eighteen days with the signs of kernicterus. It is interesting that he was given large doses of Vitamin K in the form of "Synkavit". Since then Gasser has described a further 10 cases, Allison 2 and Varadi 1 case.

The second group comprise those babies born at full-term but with numerous congenital anomalies. Willi (1947) first noted the large number of erythrocytes containing Heinz bodies in a baby who died at five days with multiple anomalies. In two other fatal cases described by Willi & Hartmeier (1950) the spleen was either absent or hypoplastic. Varadi describes the case of a full-term infant, one of twins, who became anaemic at three weeks of

age and was found to have numerous Heinz bodies in the peripheral blood but recovered following blood transfusion. This child may well be similar to that described by Cathie (1952) in which a severe Heinz body anaemia was present but no other abnormalities. Another interesting case is that investigated by Allison (1957). This was a boy who had a splenectomy for haemolytic anaemia at twenty months and in whom Heinz bodies were demonstrated in excess two years later. These three cases differ from the others in having an anaemia associated with Heinz bodies, but without other congenital abnormalities and which in one case the spleen was known to be present at birth.

At the other extreme there are a number of cases of full-term infants with Heinz bodies and multiple congenital abnormalities which do not develop anaemia. Most of these have the complex series of anomalies first described by Martin (1826), that is an atrio-ventricular communis with or without transposition and hypoplasia of the pulmonary artery, together with double inferior vena cavae, situs inversus abdominalis with a universal mesentery, absent spleen and an accessory lobe in the left lung. Such a case was seen at this Hospital in which the diagnosis was made in life when 6% Heinz bodies were detected in the peripheral blood (Cottom 1958). Similar cases are reported by Willi (1947) and Nihoyannopoulos (1957).

Our case differs from either group in that although he was born prematurely his haemolytic anaemia did not develop until he was ten weeks' old so he differs from those described by Allison (1957) and Gasser (1953). In addition he had some of the features of Martin's syndrome, but

unlike those he developed a haemolytic anaemia. A case with certain similarities was reported by Plowman (1957). This was a premature infant weighing 2550 g. at birth with duodenal atresia, he was not anaemic but an excess of normoblasts was noted. The duodenal atresia was resected but, like our case, he continued to have diarrhoea and died at the age of thirteen weeks. At autopsy the spleen was absent and he had many of the features of Martin's syndrome.

Infection in Splenic Hypoplasia

A further point of interest is that this child, at the time of his second laparotomy, was found to have a large abscess around the site of his anastomosis, and this despite seven days of penicillin and streptomycin in adequate dosage. He showed a very poor clinical response to infection, this being in part responsible for his eventual demise.

There have been several reports in the literature drawing attention to the prevalence of infection in infants with splenic agenesis or hypoplasia and also in those who have had splenectomies. Ivemark (1955) reported purulent infections at post mortem in eight of his fourteen cases with splenic agenesis. Other similar cases have been reported; septicaemia with metastatic abscess formation (Levy 1956), repeated respiratory infections (Myerson and Koelle 1956), meningitis with recurrent Waterhouse-Friedrichsen syndrome in a young adult (Polhemus and Schafer 1952) and repeated attacks of pneumonia with finally acute bacterial endocarditis (Nelson and Veale 1941). The sites of infection have varied but endocarditis, septicaemia and, in particular, meningitis have been most frequently reported. King and Shuraker (1952) reported six cases of overwhelming infection in a series of 15 infants under the age

of six months who had had splenectomies performed; four of these six had meningitis. Gellis (1954) reported three cases in which septicaemia developed several months after splenectomy. Hoefnagel (1956) reported two further cases in infants—brothers—who had their spleens removed for thrombocytopenic purpura.

Experimental evidence has been obtained both in animals and humans that splenectomy has in some way interfered with their development of an immune response. The precise relationship of purulent infection to absence of the spleen is as yet not definitely clear. However, there is certainly strong circumstantial evidence that, in infants particularly and probably to a lesser extent in children and adults, the spleen plays a role in the defence mechanisms of the body, probably through antibody formation. The findings in this case would seem to support this.

Clinical Importance of Heinz Bodies

The finding of Heinz body inclusions in erythrocytes may be helpful in a variety of clinical problems. In cyanotic congenital heart disease the existence of Heinz bodies strongly suggests that it is a definite complex of cono-truncus anomalies.

Four cases showed a remarkably similar pattern (Cottom 1958). They are characterized by bilateral inferior vena cavae, one of which drains into each atrium, there is atresia of the tricuspid valve so that blood passes to the left atrium via an atrial septal defect, thence through a mitral valve with four cusps into the left ventricle. There is a ventricular septal defect leading to a small slit-like right ventricle and into a hypoplastic pulmonary artery. The ductus arteriosus is usually open.

Heinz bodies occurring in premature babies may be associated with a haemolytic

anaemia which responds to treatment with blood transfusion and is commonly of good prognosis. On the other hand, when they occur with anaemia in babies born at full-term it is likely that there are other serious congenital anomalies.

The presence of Heinz bodies might be of use in diagnosing asplenia in cases of recurrent infection similar to those reported by Murphy & Mitchell (1957).

Finally in intestinal obstruction (as in this case) the finding of Heinz bodies makes it probable that a universal mesentery is present and that the obstruction is due to a volvulus.

Summary

1. A case of haemolytic anaemia associated with Heinz bodies occurring in a premature infant is described. In addition there was hypoplasia of the spleen, a centrally placed liver and a universal mesentery. This latter resulted in an intestinal obstruction due to a volvulus.

2. The literature on Heinz bodies associated with haemolytic anaemia and with congenital anomalies is reviewed. Reported cases suggest that in Heinz body anaemia in premature infants there is rarely any other congenital anomaly, whereas when they are found in the full-term infant, with or without anaemia, they are likely to be associated with serious congenital malformations. Commonly these follow the pattern first reported by Martin (1828) and consist of a small or absent spleen, situs inversus abdominalis, a universal mesentery, cono-truncus anomalies and often an accessory lobe in the left lung.

3. It seems probable that cases exist in which only certain features of the full

syndrome are present. We report such a case and draw attention to the diagnostic help afforded by examining the peripheral blood for Heinz bodies.

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Hydrops Foetalis without Blood Group Incompatibility but Associated with Hydramnios

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Survival from the condition known as hydrops foetalis (generalized edema, ascites and sometimes hydrothorax of the newborn) is extremely rare. The condition generally occurs in cases of Rhesus immunization and other causes of the disease are not mentioned in the ordinary pediatric text books. One infant who survived will be described in detail and four others who were also associated with hydramnios, but where no immune antibodies were found in the serum of the mothers, are presented in tabular form. A sixth case, with hepatosplenomegaly and erythroblastosis where the mother had diabetes, is also included in this article.

Case 1. The mother had an acute nephritis seven years old but had otherwise been healthy; she had given birth to two healthy children 7 and 3 years before the birth of the hydropic infant. She had an abortion in the third month of pregnancy in September 1956. There was no albuminuria during her previous pregnancies. Nothing unusual happened with the two elder siblings during the neonatal periods. The mother had never received any blood transfusions.

During the last month of pregnancy increasing edema of the lower extremities occurred and her abdomen was large and dis-

tended. Gemelli were suspected. Birth took place on the 14th of March 1958 one month before term. At the time of delivery albuminuria (0.7 per cent) and hypertension (180/100) were found. Labour lasted 12 hours. One hour before delivery the membranes ruptured spontaneously and 2500 ml of clear amniotic fluid was collected. The heart sounds were good. The head was born one half hour before delivery, but the rest of the body was only delivered after heavy traction and expression had been employed. The placenta was very large and edematous and weighed 1600 g. The infant—a girl—weighed 3900 g, length 48 cm. She was somewhat flaccid but cried immediately. Ten mg of Synkavit was given intramuscularly. The abdomen was very expanded and there was marked generalized edema. The respirations were frequent and when she cried she became cyanotic. She was transferred to the Pediatric Department. A rubber probe could be introduced 15 cm into the rectum and a little meconium pasted to the catheter. The mother was blood group A Rh positive—her serum contained no immune antibodies. Her Wassermann and Kahn reactions were negative. Her toxoplasmosis neutralization test was very weakly positive 1:10 and the toxoplasmosis complement binding reaction was negative < 1:2. The albuminuria and hypertension subsided quickly. Serum creatinine and fasting blood sugar were normal. Microscopic examination of the placenta showed



Fig. 1. Photographs of Case 1. Second day: marked generalized edema (340 ml ascites fluid had been removed on the first day). — Fig. 2. Case 1. On the twelfth day—the edema has now disappeared.

only hyperemia and edema and very few nucleated red cells were seen. The father had type O Rh positive.

The infant continued to be dyspnoeic and became very cyanotic when crying. She was placed in an oxygen tent, there was no jaundice. Roentgenogram of the abdomen showed ascites; no air was seen in the colon. Abdominal puncture was performed at the age of 18 hours; 340 ml of yellow, clear ascites fluid was removed. The specific gravity was 1.042 and the fluid contained 2% protein (Esbach), 46 mg% urea and 2.1 mg% bilirubin, only a few epithelial cells were seen by microscopical examination. The baby was somewhat relieved after the puncture but the edema tended to increase. The liver was palpable one to two centimeters below the costal margin, the spleen was not palpable. The infant had blood type A Rh neg (*cde*);

the erythrocytes were not sensitized by immune antibodies. The erythrocytes of the infant were not agglutinated by the mother's serum neither by incubation at 37°C nor using the indirect Coombs' test.

The direct Coombs' test was performed both at the blood bank of the University Hospital and at the State Serum Institute, Blood Group Department, and was negative. The hemoglobin value was 90% a few hours after birth and 75% at the age of 24 hours. Reticulocytes 9.6%. Fifty nucleated red cells were counted in the peripheral blood per 100 white cells. Leucocyte count 16,800, stab forms 6%, leucocytes 47%, lymphocytes 43%, monocytes 4%; thrombocytes 306,000. Thymol reaction negative 0.04. Prothrombin time 51 seconds (normal value for adults 18 sec). Serum bilirubin 3.8 mg%, 6 hours old and 7.7 mg% at the age of 24

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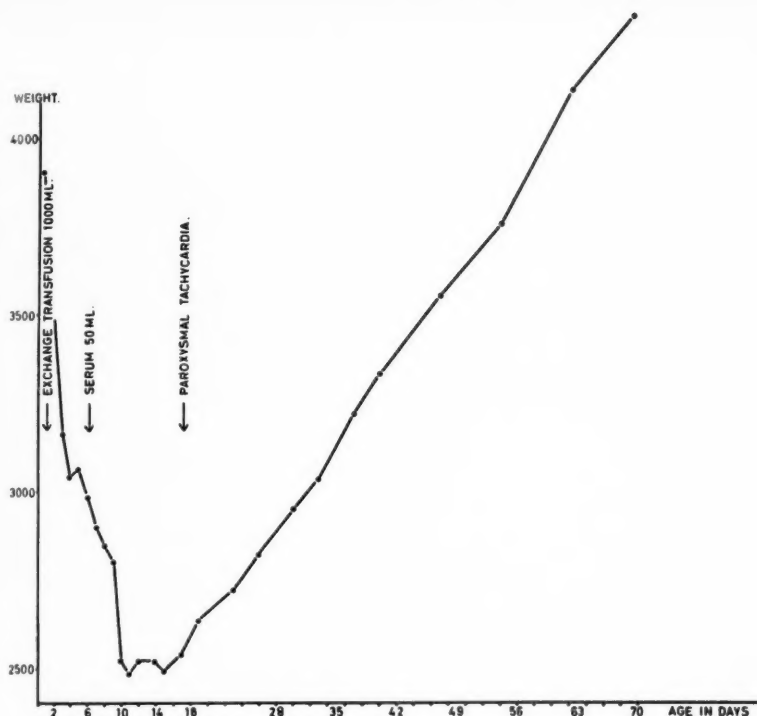


Fig. 3. Weight curve (Case 1). The infant lost 1400 g during the first 12 days.

hours. The osmotic fragility of the erythrocytes in hypotonic saline dilutions was within normal limits. Blood urea 47 mg%. Total serum protein (24 hours post partum) 3.8 g/100 ml; (albumin 1.47 g%, α_1 globulin 0.47 g%, α_2 0.53 g%, β_1 0.50 g%, β_2 + gamma globulin 0.84 g%). At the age of 25 hours an exchange transfusion using 1040 ml fresh blood from two group A Rh negative donors (same group as the infant) was performed without difficulty. The exchange transfusion was well tolerated. A total of 800 mg of calcium laevulate was given in four divided doses during the transfusion. Before the infant received the calcium laevulate injections the pressure in the umbilical vein was somewhat elevated but otherwise it was normal.

The infant received sodium penicillin

100,000 units twice a day for the first 10 days of life.

A photograph of the child on the second day of life (after ascites puncture and exchange transfusion) is shown in Fig. 1. The edema was practically unchanged by the exchange transfusion and the condition of the infant remained critical during the first three days. A roentgenogram of the thorax on the second day showed the heart to be very much enlarged with compression of the left lung. No fluid in the pleurae could be seen. Only very little jaundice was visible from the 4th to the 9th day. Serum bilirubin was 5.5 mg% on the second day of life and 1.6 mg% at the age of 3 weeks. The infant voided only very little urine during the first few days. It contained a trace of protein and on the second day a few erythrocytes. From

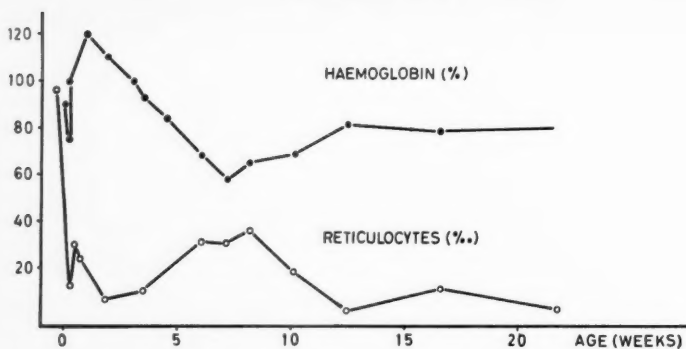


Fig. 4. Hemoglobin and reticulocyte curves (Case 1). The infant received an exchange transfusion at the age of 25 hours. Later ferrotartrate was given orally.

the 6th day on there was no proteinuria. The girl received no fluid at all during the first 4 days, when very small amounts of glucose and mothers milk were given by gavage. From the third to the tenth day 30 mg of tocopheryl acetate (vitamin E) was given intramuscularly once a day. The ascites did not recur.

On the seventh day, when the infant had lost 900 g but was still rather edematous, 50 ml of human serum was given intravenously through the tibial bone marrow.

The weight continued to decrease until the 12th day of life when it reached a minimum of 2480 g. The edema had now completely disappeared and a total loss of 1420 g had occurred. The infant had now come down to the birth weight of a 4 weeks prematurely born baby having lost 36% of her actual birth weight. From the 16th day on the infant gained weight satisfactorily. The aspect of the girl at the age of 12 days is seen in Fig. 2.

The hemoglobin and reticulocyte values are shown in Fig. 4. The total serum protein increased to 4.5 g% on the fifth day and to 5.2 g% at the age of four weeks. Serum electrolytes were not determined till the 8th day and then were normal. On the 11th day of life a lumbar puncture was done. The pressure was normal and 2 ml clear, slightly yellow, spinal fluid was obtained. The number of cells was normal, but total protein

was augmented to 116 mg%, bilirubin was 0.36 mg%.

The condition of the child was steadily improving although she still had to receive mothers milk by gavage. Suddenly on the 17th day she became acutely ill, pale and a little cyanotic with paroxysmal tachycardia—heart rate about 280 per minute (Fig. 5). The liver was felt 3 cm below the costal margin. She was treated with tinctura digitalis and digoxin for two days without improvement. On the second day procaine amide chloride (Pronestyl (Squibb)) 50 mg was given intramuscularly at 3 and 5 hours p.m. At 11 h.p.m. the ECG showed normal heart rate. Although digitalis was still given the infant two days later (20 days old) had a new attack of tachycardia with a frequency of 288. Two hours after an intramuscular injection of 50 mg of Pronestyl the heart rate was 120 per minute.

She was then put on Pronestyl 20 mg intramuscularly four times a day and from now on the heart rate has remained normal. Digitalis was discontinued on the 20th day and from the 24th day the dose of Pronestyl was gradually decreased being completely discontinued on the 35th day of life. The infant was discharged home 44 days old and has been followed regularly in the Outpatient Clinic. Apart from anemia—57% hemoglobin 2 months old—treated with oral iron medication, and a moderate umbilical hernia—

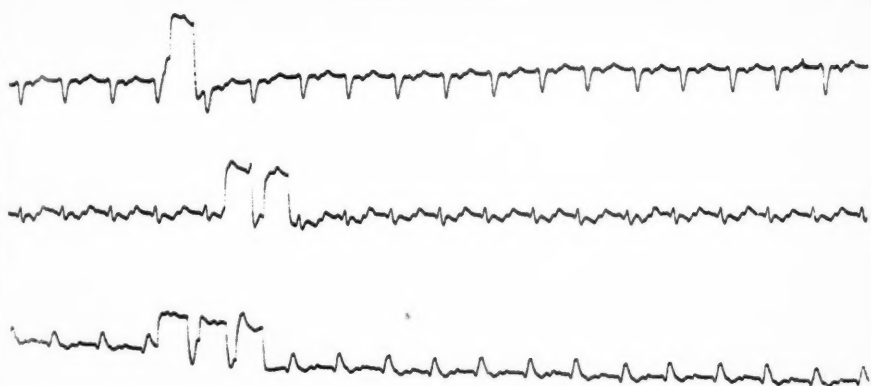


Fig. 5. (Case 1). ECG on the 18th day; supra-ventricular paroxysmal tachycardia; rate 272.

treated with adhesive plaster—the subsequent course has been uneventful. Blood urea and ECG (Fig. 6), were normal 8 weeks old. The EEG, X-ray examination of the heart and an ophthalmologic examination were normal at the age of 3 months. She could sit without support $8\frac{1}{2}$ months old (she was rather fat at that period) and walk and say 4 or 5 words at the age of 12 months, at which age she seemed to be quite normal with good intelligence and no neurological signs. Her hearing, too, was thought to be quite normal.

Summary of Case 1. The mother had toxemia and hydramnios. She lost 20 kg in weight during 16 days from the delivery of a 4 weeks prematurely born girl with very pronounced anasarca. At that time her albuminuria and hypertension had completely disappeared. The placenta weighed 1600 g and was edematous. Through abdominal paracentesis 340 ml of ascites was removed from the infant. There was erythroblastosis of the blood, and an exchange transfusion was performed. Total serum protein was only 3.8 g/100 ml. The edema disappeared slowly and



Fig. 6. Case 1. ECG at the age of 8 weeks, nothing abnormal.

TABLE 1. *Pertinent data concerning five cases of hydrops congenitus with hydramnios and one case of erythroblastosis (Case 6) where the mother had diabetes mellitus. Serological tests for syphilis were negative in all cases. Toxoplasmosis reactions negative in Case 1 to 5, not done in Case 6.*

Case number	1	2	3	4	5	6
<i>Mother</i>						
Age	32	18	27	25	28	28
Para	III	I	I	II	II	IV
Weight at delivery	87	87	66.7	74.7	—	—
Loss of weight (kg)	20	21	10	17	—	—
Abdominal circumference (cm)	110	109	93	111	103	—
Albuminuria (%)	0.7	0	0	0.2	0	0
Blood pressure	180/100	155/100	120/80	155/105	125/75	160/100
Edema	++	++	+	—	—	+
Total serum protein (g %)	—	4.8	—	—	—	6.0
Glucose tolerance curve	—	flat	normal	normal	normal	diabetes
Hemoglobin (%)	80	74	83	70	100	63
Blood group	A Rh pos.	A Rh pos.	A Rh pos.	A Rh pos.	A Rh pos.	O Rh pos.
Antibodies	none	none	none	—	none	none
<i>Infant</i>						
Condition	living	died 1 h.	stillborn	macerated	macerated	stillborn
Hydrops and ascites	+++	+++	+++	+++	+++	+
Birth weight (g)	3900	2500	2450	3100	2900	3200
Birth length (cm)	48	46	47	49	48	50
Born weeks before term	4	10?	6-8	5-6	5-6	1-2
Hepato-splenomegalia	(+)	—	—	?	?	+++
Extramedullary hemopoiesis	—	?	++	?	?	++
Blood group	A Rh neg.	—	—	—	—	O Rh pos.
Coombs' test	neg.	—	—	—	—	neg.
<i>Placenta</i>						
Weight (g)	1600	800	550	1250	2430	500
Microscopical exam.	edema hyperaemia	Langhans cells preserved	fibrosis of villi	—	many erythroblasts	—
Hydramnios (Collected ml)	+++ 2500	+++ 800+	++ 450+	+++ 8460	++ —	? —

the infant lost 1400 g. The heart was very enlarged on roentgenograms but the size had returned to normal on the 14th day of life. On the 17th day paroxysmal tachycardia with hepatomegalia supervened, successfully treated with Pronestyl. The further course has been uneventful and the child, last seen at the age of 12 months, has developed quite normally.

The most important data concerning Cases 1 to 6 are shown in Table 1.

The first five cases have in common that pronounced hydramnios (the amount of which could not always be measured) and hydrops foetalis were present. In all the six cases the serologic reactions for syphilis were negative. The toxoplasmosis reactions were negative in Case 1 to 5 but not done in Case 6. No signs of impending diabetes were found in the first five cases, whereas the mother had diabetes in Case 6. She did not follow instructions and had several episodes with

coma or insulin shock during pregnancy; in this case fetal heart sounds disappeared 15 minutes before birth. The mother had two transfusions during labour on account of bleeding from the placental margin. The infant was stillborn and had the appearance of an infant with erythroblastosis.

In only two of the six cases the mother had albuminuria at the time of delivery. No malformations of any kind were found in any of the infants, although a congenital heart disease was suspected during the first few days in Case 1. It must be admitted, however, that a detailed autopsy could not be performed on the two very macerated infants (Case 4 and 5).

The five cases of hydrops foetalis (Case 1 to 5) occurred during the years 1957 and 1958. During this period approximately 10,000 infants were delivered in the two Obstetric Departments. Only four cases of hydrops foetalis on account of Rh-immunization occurred during the same period; the cases of unknown etiology thus outnumbered the cases of erythroblastosis with hydrops foetalis caused by iso-immunization. In this connection it may be mentioned that practically all cases of Rh-sensitization from an area covering about 2 million people are referred for delivery to our Hospital.

Discussion

Iso-immunization

Since the discovery of the Rh factor in 1940 most cases of hydrops foetalis have been found to be caused by this type of iso-immunization. In the large materials of Nevanlinna (36) and of Freiesleben (14) about 30% of the infants with erythroblastosis due to Rh incompatibility were stillborn or hydropic and died shortly after delivery.

Cases of hydrops foetalis due to ABO immunization are very rare, but have been described by four authors (3, 13, 15, 39).

The *prognosis* in hydrops foetalis is ex-

tremely bad and many authors mention that most cases are stillborn and that no case has survived for more than a few hours or days. Shapiro & Cohen (45) reported hydrops foetalis with recovery in one of identical twins, the other suffering from hemolytic anemia. The infant was treated with blood transfusions and serum. Jacobi & Litvak (23) successfully treated two cases of erythroblastosis foetalis (Rh incompatibility) complicated by severe generalized edema with concentrated human serum albumin. Three other surviving infants suffering from hydrops foetalis caused by Rh immunization have been reported (9, 18, 28). Only the last case also had ascites. All three infants were treated by exchange transfusion. In one of them (18) hemiplegia supervened. O'Neill & Gordon (38) recommend the use of extended exchange transfusion. I have not been able to find any cases (like Case 1) in the literature with survival from fetal anasarca without blood group sensitization.

Erythroblastosis without iso-immunization

A clinical and pathological condition very much like that seen in erythroblastosis caused by iso-immunization has been described in cases of congenital syphilis (Henderson (20)) in cases of congenital toxoplasmosis (Zuelzer (52), Kettler (26)) and in cases in which the mother had diabetes (Miller *et al.* (33)). Extramedullary erythropoiesis and hepatosplenomegalia were found in all these conditions, but real cases of hydrops foetalis seem to be extremely rare. Persistence of Langhans' layer of cells in the placenta is only seen in cases of erythroblastosis foetalis sensu strictiori (Henderson). Berglund & Zetterström (6) found abnormally high

numbers of nucleated red cells in 9 of 19 infants of diabetic mothers during the first few days of life. The oxygen binding capacity of the umbilical blood was reduced compared with the controls, and the erythroblastosis was thought to be produced in an effort to augment the oxygen capacity. Case 6 in the present series is an example of erythroblastosis in an infant whose mother had diabetes mellitus. The liability to late toxemia of the pregnancy of the diabetic woman is well known, but in our case no albuminuria and only moderate hypertension were present at the time of delivery.

Hydrops foetalis without blood group incompatibility

Potter (40) in 1943 described 17 cases of hydrops foetalis where no signs of erythroblastosis were present at necropsy. All eleven cases in which Rh determinations were performed occurred in Rh positive mothers. Four of the 17 infants had various malformations, but in the remaining the cause was obscure. Six of the mothers later gave birth to 7 normal infants, whereas only one living infant was seen among 15 sensitized women who had previously given birth to erythroblastotic hydropic infants. She does not mention whether hydramnios or toxemia were present in the cases of unknown etiology. Hydrops foetalis without detectable blood group incompatibility has also been reported by Hartenauer (17) and Sachweh (44). They made no mention of albuminuria in the mother or hydramnios. Both mothers had previously given birth to stillborn infants or had abortions. Sachweh's infant had a hemoglobin of 56 %

and was treated by exchange transfusion but died a few hours old.

Toxaemia gravidarum

Nyhoff (37), Dorland (11) and Javert (25) indicate that edema and albuminuria are often present in the mother in cases of hydrops foetalis. Thus Nyhoff (1911) found albuminuria in 30 % of about 60 cases collected from the literature including 4 of his own, and Javert mentions that there was a high incidence of pre-eclamptic toxemia in the mothers among his 16 cases of hydrops foetalis. Bromberg & Polishuk (7) in 1948 reported the interesting occurrence of two hydropic stillborn infants in a woman's first and fourth pregnancies which were associated with severe toxemia. No maternal immunization or signs of fetal erythroblastosis were found. No mention of hydramnios was made. The second and third pregnancies unassociated with toxemia terminated in the delivery of two normal infants.

Fetal ascites

Fetal ascites, which was present in Case 1 to 5, can be found without edema, but since the condition is often accompanied with more or less pronounced edema, especially of the abdominal wall, the external genital region and of the lower extremities, it seems to me, according to the literature, that differentiation between cases of fetal ascites and hydrops foetalis is not always easy.

Lord (29) reported 2 cases with urinary tract obstruction and reviewing the literature found such obstructions to be the most common cause of fetal ascites. In 1958 Silver *et al.* (47) collected a total of 107 cases from the literature and added one case of their own. Only five cases of fetal ascites seem to

have survived. One of these cases had an obstruction of the posterior urethra and was successfully operated (James & Davis (24)); another had portal cirrhosis of the newborn and was treated with repeated paracenteses (Bellin & Bailit (5)). Silver *et al.*'s case and that of Minkowski *et al.* (34) were also treated with abdominal paracentesis. The infants lost 1200 and 800 g respectively. The cause of the ascites (and edema) was obscure in both cases, but it is interesting that hydramnios was present in the case reported by Minkowski *et al.* This infant had an aspiration pneumonia at the age of 3 weeks with heart failure and sudden enlargement of the liver. According to their description it might well have been an attack of paroxysmal tachycardia like that seen in Case 1 of the present material.

Other rare causes of fetal ascites are fetal peritonitis (22, 43), chylous ascites (49) and a ruptured ovarian cyst (48). The ascites is not seldom so extensive as to cause dystocia with spontaneous rupture of the abdominal wall (Dorland) or necessitating surgical perforation (4, 31). The *nephrotic syndrome* is very rare in the newborn (16, 21, 27).

Hydramnios

Nyhoff (37) found hydramnios in 19 of 48 cases of fetal hydrops universalis. An interesting analysis of 145 cases of hydramnios has been reported by Prindle *et al.* (42). They found a high incidence of pre-eclampsia in the mothers, of abnormalities of the placenta and of stillbirth and malformations in the infants. No less than 23% of these had anencephaly. The authors do not mention the occurrence of hydrops in any of the infants. De Young (50) found pronounced hydramnios in 8 cases of atresia of the upper part of the gastrointestinal tract of the newborn. Most authors think that the fetus swallows the amniotic fluid, which is then absorbed from its intestinal epithelium. Davi & Potter (10) by injecting Thorotrast

into the amniotic sacs of pregnant women just prior to therapeutic abortion, found that the contrast material not only appeared in the tracheobronchial tree, but that the entire gastrointestinal tract was outlined. Interesting theories and experiments concerning the origin of hydramnios have been reported by Minkowski *et al.* (34) and by Loyd & Clatworthy (30). The origin may either be 1) fetal, 2) amniotic or 3) maternal. A very rapid exchange of water between the maternal circulation and the amniotic fluid has been found in experiments with heavy water and radioactive sodium. The cause of hydramnios is probably mainly due to abnormal permeability of the placenta (34).

In the *pathogenesis of hydrops foetalis* low serum protein values are generally considered to be important. Javert (25) found a total serum protein of 3.4 g/100 ml in one mother and only 1.9 g/100 ml in her hydropic infant. Jacobi *et al.* found 5.2 g%, Minkowski *et al.* 5.4 g%, Silver *et al.* 4.3 g%, and Richdorf & Cady 4.2 g% in their infants. Unfortunately the serum protein value was only determined in one of our infants (Case 1) where it was 3.8 g% and in two mothers who had 4.8 g% and 6.0 g%. Silver *et al.* found high serum transaminase and alkaline phosphatase values in their case. Zollinger (51) thinks damage of the capillaries plays an important role in the development of hydrops foetalis. Heart failure may also be significant (38).

Abnormalities of the placenta

The placenta was very large in 4 of our 5 hydrops cases. According to Eastman (12) the normal full term placenta weighs about one-sixth as much as the child, that is, about 500 g. The most important changes found by microscopical examination are seen in Table 1. The pathological

alterations of the placenta in 16 cases of hydrops foetalis have been described by Hellman & Hertig (19); in cases of icterus gravis also associated with erythroblastosis the changes of the placenta were less severe. The microscopical changes in the placenta of some of our cases could possibly bring about difficulties in the transfer of water etc. from the fetus to the maternal circulation and explain the hydrops and hydramnios. Even if this hypothesis holds true the cause of the placental pathology remains obscure.

Toxemia of pregnancy could play a role, but in our experience the infants of eclamptic or pre-eclamptic mothers are generally dehydrated, quite contrary to our cases.

Paroxysmal tachycardia in the newborn

Our Case 1 had two attacks of supraventricular paroxysmal tachycardia 17 and 20 days old. The size of the heart had returned to normal on chest roentgenograms before these attacks, and it was not altered when a new picture was taken the day after the last attack. One can only speculate if edema was present in some parts of the heart just after birth and the disappearance of this edema caused the tachycardia. If the assumption, that Minkowski & colleagues' infant also had paroxysmal tachycardia at the age of three weeks, is right (the infant had at that time a respiratory rate of 110 so that it was probably impossible to count the heart rate) an analogous case has occurred. Most of the cases of paroxysmal tachycardia published in infancy were idiopathic and supraventricular (2, 35). Anderson & Adams (1) collected eleven cases diagnosed

antenatally. Generally digoxin is considered to be the best drug in the treatment of paroxysmal tachycardia in infants. Christensen (8) had good results after intravenous injections of strophanthin in his two cases and Mannheimer (32) stopped the attacks by subcutaneous injections of neostigmin. Sher (46) gave up to 100 mg of procaine amide intravenously to a two months old infant with prompt result. Intramuscular injections of 50 mg of procaine amide were very effective in our own case.

Summary

Five cases of hydrops foetalis without blood group sensitization born in 1957-58 are reported. The mothers had hydramnios but only two of them had a little albuminuria. In four cases the placenta was very large. Syphilis and toxoplasmosis were not present. The cases are presented in Table 1, in which a case of erythroblastosis where the mother had diabetes but no iso-immunization, is also included. Only one of the infants survived after abdominal paracentesis and exchange transfusion. The infant lost 36 % of its birth weight. At the age of 17 and 20 days attacks of supraventricular paroxysmal tachycardia occurred and were successfully treated with procaine amide injections. The infant was healthy and normal at the age of 12 months. Decreased permeability of the placenta might explain the hydramnios as well as the anasarca of the fetus. The incidence of hydrops foetalis of unknown etiology is no doubt higher than indicated in the literature, since such cases are probably seldom reported.

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SUMMARY OF SUPPLEMENT

Free Erythrocyte Copro- and Protoporphyrin

A Methodological and Clinical Study

by LARS WRANNE

(Supplement 124)

A method for the simultaneous determination of free erythrocyte copro- and protoporphyrin is described. Coproporphyrin is determined fluorometrically after a final extraction with 0.24 *N* HCl, while protoporphyrin is determined spectrophotometrically after a final extraction with 5 *N* HCl. The details of the analysis have been investigated and recovery experiments performed. Since losses of porphyrins always occurred, suitable corrective equations were used.

The nature of the extracted porphyrins was checked. Protoporphyrin was identified in the 5 *N* HCl extracts. In the 0.24 *N* HCl extracts, the identity of coproporphyrin could be experimentally corroborated.

In healthy male adults, the mean concentration of free erythrocyte protoporphyrin was found to be 30 $\mu\text{g}\%$ and that of coproporphyrin 1.3 $\mu\text{g}\%$. The corresponding mean values in females were 37 $\mu\text{g}\%$ and 1.2 $\mu\text{g}\%$.

Divergent values were found in early infancy. In cord blood, the content of free protoporphyrin was 54 $\mu\text{g}\%$ and that of coproporphyrin 2.8 $\mu\text{g}\%$. During the

first week of life, the latter concentration decreased rapidly; in infants 1–2 weeks old, the mean concentration was down to 0.9 $\mu\text{g}\%$. The free protoporphyrin remained nearly unchanged during the first four months of life. After that, fluctuating values supervened. Beginning about the age of one year, the values approached those for normal adults.

The free protoporphyrin has also been studied in erythrocytes from iron deficiency patients before and during iron therapy. The protoporphyrin concentration decreased considerably during treatment.

In plasma, a coproporphyrin-like pigment has been found. The mean concentration in adult plasma corresponded to 0.8 μg coproporphyrin per 100 ml. In cord blood plasma, the concentration corresponded to 1.5 μg per 100 ml.

The findings are discussed and put in relation with other known physiological processes during infancy. The conclusion is drawn that erythrocytes of the very young infant deal with the free protoporphyrin in a dissimilar manner from that of the adult's erythrocytes.

PROCEEDINGS OF PEDIATRIC SOCIETIES

Norwegian Pediatric Society

Meetings Sept. 18-19, 1959

O. Cardborg: Cytomegalic inclusion body disease

A boy of 10 weeks of age was admitted to the Pediatric Department of Oslo University Hospital with diagnosis of atresia of the bile duct. The patient was born at term after a normal pregnancy. Birth weight 2340 g. He was listless at birth, with a weak cry, and was given oxygen treatment during the first two days of life. In the course of the first day of life icterus and cutaneous hemorrhages were observed. No evidence of erythroblastosis was found. On the 12th day of life hepatosplenomegaly was demonstrated. Since then the icterus had persisted and the stools were claycolored. When he was four weeks of age cortone was given for a week in doses of 25 mg per day without any demonstrable benefit. On admission to the Pediatric Department the patient was markedly dystrophic and icteric. Weight 2420 g. Considerable enlargement of the liver and spleen was demonstrated. Laboratory examinations revealed severe anemia, reticulocytosis, leukocytosis and immaturity of the neutrophils, thrombocytopenia, a markedly elevated sedimentation rate, hyperbilirubinemia, and hypoprothrombinemia. Coombs' test was negative, as were blood culture, the dye test, and the Meinicke test. Examination of urine and spinal fluid with a view to inclusion bodies also gave negative results. Examination of the eyes disclosed numerous, evenly distributed opacities in the vitreous body on the left side, while the right eye was normal. During his stay in hospital the patient was treated with penicillin and chloromycetin in sepsis doses. After a little over three weeks an acute exacerbation of the condition set in; hemoglobin values fell

steeply in spite of high reticulocyte values. Blood transfusions were of no avail, and death occurred less than 4 weeks after admission to hospital. *Autopsy* revealed typical inclusion bodies in sections from salivary glands, lungs, and kidneys.

The patient represents the first case of "Inclusion Body Disease" diagnosed in Norway. The disease should be born in mind whenever a combination of icterus and thrombopenic purpura is observed in newborn infants. Recent years' reports on cases cured after treatment with cortisone compounds make it doubly important that the diagnosis be made *intra vitam*. (The case will be published.)

A. Sundal: Treatment of urinary tract infections in children

(To be published in *Medicinsk Årsbok*, 1959/60, Munksgaards Forlag, Copenhagen.)

O. K. Harlem: Pheochromocytoma with secondary hydronephrosis

R. S. was almost 9 years old when she was admitted to the Pediatric Department, Haukeland Hospital, Bergen, in August 1958 with proteinuria. She comes from an allergic family and had been treated for asthma in the hospital 18 months previously. At that time blood pressure was normal. For a few months prior to admission she had been ailing, had complained of nausea and backache, had sweating bouts, poor appetite, and had lost weight. On admission she was thin, but did not seem particularly ill. Blood pressure: 155/105. There was proteinuria, but neither hematuria nor cylindruria. Renal function tests were normal. During

her stay in the hospital her blood pressure was rising. Ophthalmoscopic examination, which on entry revealed fundus hypertonicus of the first degree, 3 weeks later revealed fundus hypertonicus of the fourth degree. Intravenous urography showed non-function on the left side. Retrograde pyelography showed that the left renal pelvis and ureter down to the region between the middle and lower third were markedly dilated. Adrenalin-noradrenalin excretion in the urine was considerably elevated. The regitine test was positive. Palpation of the left side of the abdomen brought about a significant rise in the blood pressure. Roentgenographic examination with presacral oxygen injection showed normal adrenal glands.

The patient's symptoms could be explained by the presence of a hormone-producing chromaffin tumor in the region between the middle and lower third of the left ureter, associated with secondary hydronephrosis. She was operated upon, and a walnut-sized pheochromocytoma, encircling the left ureter and the iliac vessels at their crossing, was found. The left kidney with the upper two thirds of the ureter had to be removed, together with the tumor and the iliac vein. The postoperative course was uneventful. She was given a continuous noradrenalin drip for three days.

One year after the operation the patient is free from symptoms, has a normal blood pressure, and normal adrenalin-noradrenalin excretion in the urine. The changes in the fundus have practically disappeared. It is an interesting phenomenon that while the symptoms from the pheochromocytoma were manifest the patient had no allergic attacks. After the operation the allergic symptoms have reappeared.

Eyvinn Tveterås: Acute osteomyelitis in childhood

During the years 1951-1959, 29 children—15 boys and 14 girls—were treated for acute osteomyelitis in the Pediatric Department, Haukeland Hospital, Bergen. The incidence of the disease in infants under one month of age has risen markedly inasmuch

as 9 out of 11 patients in this age group were admitted to the hospital during the past two and a half years. The most common locations were the femur, tibia, humerus, and maxilla. In 20 infants positive roentgenographic findings were present. Four of the remaining nine patients had maxillary osteomyelitis. Bacteriological diagnosis was made in 20 cases. The findings were: staphylococcus aureus in 18 cases (90 %), and group B hemolytic streptococci in two cases (10 %). Antibiotogram performed with 12 staphylococcus strains revealed penicillin resistance in 7 cases while all strains were sensitive to tetracyclines, chloramphenicol, and erythromycin. The diseases most likely to be confused with osteomyelitis are: rheumatic fever, cellulitis, and suppurative arthritis. One patient had been believed to be suffering from osteomyelitis for quite a while when an osteogenic sarcoma was demonstrated. Penicillin in large doses combined with another antibiotic, preferably chloromycetin or erythromycin, has been the treatment of choice. On an average the duration of treatment was a little more than 6 weeks. Surgical intervention was limited to drainage of soft tissue abscesses. None of the patients in the series died. In one patient, with osteomyelitis of the femur, necrosis of the head and shaft of the bone developed. In another infant the caudal metaphysis of the radius is affected. These are the only two patients still showing limited functional ability.

J. Steen and K. Bie: Empyema in children under two years of age

During the period September 1957 to May 1959 eight cases of staphylococcal empyema in children less than two years old were treated in the Pediatric Department and Surgical Department III, Ullevål Hospital. A ninth patient with this condition died on the way to hospital. Six of the patients contracted the illness during the early months of 1959. Two of the patients were almost two years old; the others were infants of under five months old, four of whom were less than 10 weeks old. These younger infants had only presented with slight respi-

ratory embarrassment and no fever prior to admission. Most of the patients were in poor condition on admission, with elevated temperatures. All the patients but one, who was moribund on admission, had marked leucocytosis. In all cases the diagnosis was verified by pleural puncture and bacteriologic examination revealing staphylococci. In five patients the empyema was left sided, in the remaining cases right sided. The microbes were penicillin resistant except for one strain, while all strains were sensitive to erythromycin and chloromycetin. Roentgenographic examination disclosed pyopneumothorax in three patients, while the emphysematous blebs, at times large in proportion, which are characteristic of staphylococcal pneumonia were demonstrable in the other patients. The last follow-up roentgenographic examination revealed normal findings in six cases. The remaining two patients had some degree of residual infiltration and pleural thickening. The medical treatment was standardized as much as possible: penicillin was administered in doses of approximately 500,000 units per kg of body weight, together with erythromycin in doses of about 100 mg per kg of body weight. Four patients were given chloromycetin for a shorter period, another one cathomycin. Surgical treatment was instituted as soon as the diagnosis had been verified. The first patient was treated by repeated aspirations; but on the others thoracotomy was performed followed by suction drainage lasting from 7 to 42 days.

N. J. Jølster: Pitressin resistant diabetes insipidus

A 12-year-old girl was admitted to the Pediatric Department of Oslo University Hospital with polydipsia and polyuria. Generally, she had been healthy as an infant and, in particular, she had not needed more fluid administration than is normal for her age. There had been no incidence of dehydration. Apart from a period of eczema at about two years of age and a moderate asthma at about five years of age, the patient

had never been seriously ill until the onset of her present disease. However, since becoming old enough to ask for water herself, she had been drinking rather a lot. Her fluid intake had gradually become considerable, and urinary output had risen accordingly. On admission, diuresis and fluid intake varied between 5 and 10 l a day. The patient was well nourished, and the general somatic examination was negative. The specific gravity of the urine ranged between 1001 and 1003, and repeated tests showed the urine to be chemically and microscopically normal. Blood electrolytes were normal and there was no urea retention. Creatinine tolerance, creatinine clearance, urea clearance, and T_m PAH were within the normal range. No increase in the specific gravity of urine, nor decrease in urinary output was brought about by intravenous infusion of hypertonic saline solution, concentration tests, or subcutaneous injection of aqueous pitressin in adequate doses. The presence of a diabetes insipidus syndrome of the pitressin-resistant type was thus established. Because of the negative family history and the normal infancy, congenital renal diabetes insipidus could be excluded. Supplementary examinations justified the elimination of hypokalemia, hypercalciuria, and nephrocalcinosis, the Fanconi-Lightwood syndrome, the ordinary chronic kidney diseases, and urinary tract obstructions as possible causes of the pitressin resistance. Pituitary diabetes insipidus could be eliminated in view of the negative response to pitressin, even though transient pitressin resistance has been observed in this disorder. The condition is interpreted as a primary polydipsia. The possibility of an injury to the concentration centre cannot be ruled out, but the patient had no symptoms of cerebral damage. Strong indications of psychogenic polydipsia or "compulsive water drinking" were, however, present. It has been demonstrated, experimentally by de Wardener and Herxheimer, and clinically by various authors, that protracted polydipsia leads to functional pitressin resistance and clinical diabetes insipidus. It is well known that the

diagnosis of this condition is difficult since it is based, in the first place, on elimination of other possible disorders and, secondly on a therapeutic trial which depends on the patient's cooperation. Therapy involving the gradual reduction of fluid intake over a period of six months is now being tried in our patient. The pitressin resistance in "compulsive water drinking" being reversible, it is to be expected that the concentration ability will improve parallel with the reduction in the fluid intake.

Serre Halvorsen: Galactosemia: a case with renal tubular changes

In the Pediatric Department of Oslo University Hospital we have recently had a fatal case of galactosemia. The patient was a 16-month-old boy. There was no known case in the family. On admission he had marked hepatomegaly and slight icterus. Laboratory investigations showed proteinuria, galactosuria, cylindruria, aminoaciduria, a low PP, increased galactose levels in the serum and spinal fluid, low serum calcium and phosphorus values, and a marked roentgenological osteoporosis. He was put on a lactose-free diet as soon as the diagnosis was made, and the liver decreased rapidly in size, but the general condition did not improve, and he died of meningitis. The *autopsy* showed liver changes, said to be typical of galactosemia; large, vacuolized liver cells with abundant fat, fibrosis and an "acinous" arrangement of the liver cells. The kidneys also showed pathological changes. The proximal tubules were dilated, with flat, atrophic epithelium. The tubular cells showed more eosinophilic staining than usual and showed coarse granules. The distal tubules showed similar changes, but less marked. Calcium depositions were found both in the tubular cells and in the interstitial connective tissue.

Renal changes in galactosemia have previously been described in a few papers only. The changes have been similar to those reported in our case, and one case has had nephrocalcinosis. It is postulated that the osteoporosis which is an almost constant

symptom in galactosemia, is secondary to the tubular damage.

J. Olsen: Hereditary spherocytosis with kernicterus

Kernicterus as a result of hereditary spherocytosis has only been reported three times previously. The following is a report of a patient with this condition, admitted when six days old to the Pediatric Department, Haukeland Hospital, Bergen. The patient's paternal grandmother, father and five of the latter's sisters and brothers, and a cousin of the infant all have hereditary spherocytosis. (Six have undergone splenectomy.) Pregnancy and delivery were normal. Birth weight 2970 g. No icterus was observed at birth, but the infant gradually became increasingly jaundiced, and distinct signs of kernicterus developed. On admission, symptoms of kernicterus were present. Hemoglobin 100 %. Reticulocytes, 20 %. Serum bilirubin (indirect), 42.3 mg %. Blood smear, spherocytosis. Mother and infant blood group, O, Rh-positive. Coombs' test, direct and indirect, negative. The fragility of erythrocytes when tested in hypotonic saline solutions was normal. Two blood exchange transfusions were performed, after which serum bilirubin gradually fell to normal values. At 10 weeks, 14 weeks, and 6 months old the fragility of the red cells was normal both at room temperature and after incubation; but at about 19 months old partial hemolysis occurred in 0.80 % and complete hemolysis in 0.38 % of sodium chloride solution after incubation at 37° for 24 hours. At room temperature the figures were 0.60 % and 0.38 % respectively. The spleen was not noticeably enlarged. The patient presented the picture of severe motor retardation with typical athetosis. Blood incompatibility between mother and infant could be eliminated as the cause of the patient's icterus. The negative Coombs' test in no way supports a hemolytic mechanism caused by an antigen-antibody reaction. The frequent familial occurrence, the anemia, icterus, spherocytosis, and the increased fragility of the erythrocytes support the diagnosis of hereditary spherocytosis.

Olav Trygstad: Gargoylism, dysostosis multiplex. Hurler's syndrome

Two patients with typical gargoylism were demonstrated, both admitted to hospital at about the same time. They are the only two patients with this diagnosis who have been admitted to the Pediatric Department in Bergen since its inauguration in 1950. The patients were two girls aged 21 and 26 months referred to the hospital for observation because of hypothyreosis (?), kyphoscoliosis, umbilical hernia, and mongolism (?). The parents had noticed nothing untoward about the patients although the "key symptoms", i.e. chronic rhinitis, umbilical hernia, and kyphoscoliosis had made their first appearance at about six months of age in both cases. The clinical and roentgenographic picture presented by both patients revealed the disorders typical of gargoylism. Both had hepatosplenomegaly and corneal opacity (slit lamp). The roentgenographic findings were pathognomonic, disclosing kyphoscoliosis in the dorsolumbar region, the vertebral bodies presenting biconvex bearing surfaces and a wider anteroposterior diameter caudally than cranially. In both cases a pathologic, flat blood sugar tolerance curve with low-fasting blood sugar was found, while the adrenalin tolerance curve and galactose tolerance were normal. The younger patient showed the characteristic granulation of the lymphocytes: an incomplete manifestation of the Alder anomaly (the Gasser type). In the elder patient cystinuria was demonstrated. At the present time the disorder is regarded as "an inborn error of metabolism"; specifically, a disturbance of mucopolysaccharide metabolism (chondroitin-heparin metabolism).

Dag Skyberg: Primary cerebral sinus thrombosis

A 9-month-old girl was admitted to the Pediatric Department, Ullevål Hospital with gastro-enteritis. On admission, she was markedly dehydrated and drowsy, with uniform rigidity of the musculature and continuous synchronous muscular tre-

mors. Intravenous fluid therapy resulted in a rapid amelioration of the condition; but a few days later a series of epileptiform fits with generalized convulsions and loss of consciousness began. The attacks abated under barbiturate and chloral hydrate medication. The following day, edema of the forehead and anterior part of the parietal region developed, subsequent to a visible dilatation of the veins in the same area. The EEG revealed generalized cerebral dysrhythmia fully compatible with the clinical diagnosis, i.e. primary cerebral sinus thrombosis. (Differential diagnostic possibilities were eliminated after examination of spinal fluid, tympanic membranes, sinuses, electrolytes, and blood sugar.) In addition to the antiepileptic drugs anticoagulants were administered after the patient's convulsions had subsided. A steady improvement resulted, the EEG became normal, and the infant could be discharged from the hospital five weeks after admission in good condition with no symptoms of mental or motor impairment. In the literature the prognosis of this disease is described as dubious, with a high fatality rate and grave sequelae for the survivors. That the above-mentioned patient reacted so favourably to the therapy should encourage the use of anticoagulants at the earliest moment possible. Prophylactically it is of primary importance to supervise the fluid balance in patients suffering from gastro-enteritis, morbus coeruleus, anemias, burns, and cachectic conditions resulting from infection.

Nils Alvsäker: Epilepsy in children: etiology and prognosis

Epilepsy is not uncommon in children, and 6% of the patients in the Pediatric Department, Bergen, are epileptics. This investigation comprises 365 epileptic children admitted to the Pediatric Department during the years 1950-1958. There were 182 boys and 183 girls. Sixty-eight per cent of the patients had grand mal seizures, 7.5% had psychomotor attacks, 6% had petit mal variants (myoclonic and akinetic spells), and 1.5% had petit mal absences. In the

remaining 17 % a combination of various seizure patterns was observed. In 32 % of the patients, the first epileptic attack occurred before the child was 1 year old, and in 72 % the first attack occurred before the child was 5 years old. Epilepsy was no more frequent in first-borns than in later-born babies. Perinatal complications occurred in 40 % of the cases and would thus seem to be of etiologic significance. In 10 % of the patients the epilepsy was the result of post-natal brain injuries. In slightly more than half of the cases no cause could be demonstrated. In these cases familial occurrence of epilepsy was 22 %, compared to 5 % in the others. The EEG was negative in 12.5 % of the patients. Pneumoencephalography was carried out only when special indications were present. Pathologic changes were demonstrated in 30 % of these patients. Of the mentally normal children with grand mal attacks 70 % were rendered free from seizures. A good effect was obtained in 93 % of the cases. Results were less satisfactory with regard to mentally deficient children. Freedom from seizures was obtained in 40 % of the patients suffering from psychomotor attacks. In 30 % of these cases the treatment had no effect. Phenantoin has been the drug of choice in the treatment of these two seizure patterns in doses of between 3 mg and 7 mg per kg per day. No serious complications were observed with this dosage. The results of the treatment of petit mal variants were poor, no drug being of much avail. The observation period is from 1 to 5 years. For mentally normal children suffering from epilepsy the prognosis must be considered as good. In cases where mental changes and retardation are the dominating features the prognosis is very gloomy, and these children represent a grave social problem.

DISCUSSION.—*Dr. Arne Kåss:* It is pointed out that the EEG which is such a significant help in epilepsy from a diagnostic, therapeutic, and prognostic point of view, must be carefully appraised according to case history and clinical findings.

Not only may the EEG be negative in unmistakable cases of epilepsy, the findings may also, it is stressed, vary considerably from one recording to the other in the same patient. As an illustration, comments are made on, and records shown which relate to patients in whom the EEG, on the one hand, became markedly more pathologic in the course of a clinically satisfactory anti-epileptic treatment and, on the other, became positive for the first time as much as two and a half years after the last symptom of epilepsy had been observed, in spite of repeated recordings.

N. J. Jølster: Incontinentia pigmenti: case report

The patient was the first child (girl) of a healthy mother. At the delivery it was noticed that the infant had a papulo-vesicular exanthema on the lower extremities. The rash was treated as a pyoderma without effect. The general condition was unaffected, and the blood tests were normal. In the first weeks of life there were apparently spontaneous remissions and exacerbations of the rash. At the age of one month it was first noticed that she had a blood eosinophilia (44 % of 17,000 wbc). The bone marrow also showed eosinophilia. The vesicles were sterile and contained many eosinophil cells. The exanthem became more and more symmetrical with groups of efflorescences on the median side of the thighs, and laterally on the trunk. The vesicles disappeared and the papulae were more hyperkeratotic and more like verrucae. There was a tendency to linear arrangement of the rash and some increase in pigment. The eosinophilia disappeared gradually. During the last months of the first year the rash again changed characteristically and at the age of one year she had only some pigmented streaks left in the lateral areas of the trunk. Psychomotor development, dental development, EEG, eye examination, and dental and skeletal X-ray studies were all normal. The diagnosis of incontinentia pigmenti was based on the well defined and typical three stages of the disease; the vesiculous, the verrucous and

the pigmented stage. This is the first case of incontinentia pigmenti described in Norway.

Arne Kåss: Chyloperitoneum

A boy who, according to the mother, was born with a very big stomach was admitted to hospital when 10 weeks old with an inguinal hernia. The abdomen was extremely distended and symptoms of ascites were present. During the operation about 2 l of chylous, milky fluid was tapped through the hernial sac. Clinical and roentgenographic examination, including tomographic examination of the thorax and abdomen, gave no evidence of obstructive processes. Various supplementary chemical blood tests revealed nothing pathologic. That the causative factor should be traumatic seemed highly improbable. One could only suppose that the condition was congenital, probably the result of an anomaly. A reaccumulation of ascitic fluid occurred; in all, paracentesis had to be performed six times. On the first occasions, 500–1000 ml of fluid was tapped; but at the last tapping only 120 ml was evacuated. The exudate had

the appearance of milk, and microscopy revealed a very high fat content, but no characteristic cells. Chemical examination of the ascitic fluid showed total protein values between 3.1 % and 4 % and total fat values between 14.3 % and 16.2 %. The infant's general condition was good, apart from the last few days prior to each tapping, when subjective symptoms appeared. However, as serum protein showed somewhat declining values, and the infant's growth was unsatisfactory, surgical treatment had more or less been decided upon after the last tapping; but no reaccumulation of ascitic fluid occurred. During the ensuing seven months' observation period the infant has been completely well. The general condition has been excellent, physical development normal, and general somatic examination has revealed nothing pathologic. The cause of the patient's condition will thus have to be guesswork. It is possible that a delayed canalization of the thoracic duct can explain the phenomenon. On the other hand, Nature may have cured the condition by a reproduction of the lymphatic vessels.

Danish Paediatric Society

Meeting Sept. 9, 1959

Erik Ryssing: Spontaneous Neonatal Pneumothorax.

Two cases of spontaneous neonatal pneumothorax are reported. One developed after a normal delivery and disappeared seven days later. The other occurred in an asphyctic infant who was treated with artificial positive-pressure respiration using a mask and balloon. The infant died 37 hours after birth. At autopsy a left-sided pneumothorax was observed, interstitial pulmonary emphysema with small subpleural air bullae, nearly total atelectasis and left-sided suprarenal haemorrhage were found. The etiology, pathogenesis, symptoms and treatment are reviewed. The danger of complicating rupture of alveoli in the use of artificial re-

spiration in the treatment of neonatal asphyxia is discussed. It is concluded from studies of the literature that the changes in pressure which occur normally with the initiation of normal respiration are capable of producing alveolar rupture should extensive alveolar ectasia develop because of considerable parts of the lungs offering significant resistance to expansion. Under these conditions, therefore, artificial respiration either with positive or negative pressure may produce alveolar rupture even if the pressures are maintained within physiological limits. If the pressure is increased to overcome the resistance offered by atelectatic lungs the danger is also increased. If the duration of the pressure is simulane-

ously reduced, this is tolerated better, but the margin of safety is probably very narrow.

DISCUSSION: *A. Biering:* Pneumothorax cannot be demonstrated by the usual autopsy technique and it is, therefore, possible that it may occur as an undetected complication of atelectasis. In the Department of Patho-

logy, the University Hospital, 100 serial autopsies upon infants from the maternity departments were undertaken in which the thorax was opened under water. Not a single air bubble was demonstrated with this technique so pneumothorax is probably not so very common.

Meeting Oct. 14, 1959

Welfare Director N. E. Bank-Mikkelsen: The Position of Children under the New Mental Deficiency Act.

From 1.10.1959 The Danish Mental Deficiency Act will be altered by law so that it will be administered by a board as a coordinated unit in which the central administration is in Copenhagen. Otherwise, as much decentralization as possible will be undertaken so that the entire country will be subdivided into seven centres each of which is led by medical, pedagogical, social and administrative-economic authorities. It is intended that these centres should be self-sufficient as far as possible but they are not yet completely organized.

DISCUSSION: *P. Plum:* Is it intended that notification concerning a mentally subnormal child should not involve intervention from the public authorities? It would be of importance if doctors could be attracted by the possibility for scientific work. Can the present paediatric departments not be employed as centres for diagnosis? — *Oluf Andersen:* The bad reputation surrounding the care of mental defectives probably originates from the poor set-up. Conditions will probably improve with better outer framework, better qualified personnel and access for doctors with various specialities. — *A. Dupont:* The architectural conditions of institutions require considerable improvement. The scarcity of medical attention hampers the daily work so that scientific work must wait until the elementary medical conditions have been arranged. — *S. Brandt:* Is it not possible to modify the notification forms so that the unfortunate conditions which have actually been the reason that a number of doctors have been reluctant to

notify cases are avoided? Do teachers in primary schools receive any instruction in the teaching of slightly mentally subnormal children? Is it possible to place slightly mentally subnormal children with other handicaps in a special school where the physical handicap will be catered to? — *P. W. Bræstrup:* The forms at present in use are extremely bad and should be replaced by more modern forms. — *N. E. Bank-Mikkelsen:* The circular on compulsory notification is not yet available but it will probably retain compulsory notification to the extent existing at present, i.e. notification in cases in which help under the Mental Deficiency Act is required. Compulsory school and vocational education applies to all mental defectives but the authorities determine how this requirement can be fulfilled in the case of the individual child. There are only two conditions for receiving help, viz, that the individual belongs to the district covered by the law and that he requires help. The formation of a special smaller department where primarily scientific work could be conducted without hindering research elsewhere has been considered. When a child has been notified for care under The Mental Deficiency Act, the parents will be visited by a doctor or a health visitor who will offer assistance. On the other hand, investigations via social service authorities will now be abandoned as regards the establishing of out-patient care as all such assistance is now free of charge. It will, however, still be necessary to call upon the social service authorities if the establishing of residential care is considered but the parents may avoid this if they are prepared to defray the costs themselves.

Meeting Nov. 11, 1959

Reports from The Congress in Montreal.**J. Vesterdal: Introduction.**

The well organized Congress was as large as the Congress in Copenhagen in 1956. The most important drawback with such a large congress is that one cannot find the people one wants to speak to. Attempts must be made to solve this problem in future congresses. An excellent thing which might be introduced to good advantage in future congresses was a "summing up" at the conclusion of the congress in which the leaders of the meetings and the round-table conferences each gave a review of the new developments which had appeared in their particular fields. This increased the possibilities for all-round orientation which are otherwise difficult to establish at a congress with numerous parallel sections.

P. W. Braestrup: Nutrition.

The question of nutrition in its widest sense took up a considerable part of the time of the congress. There were daily meetings concerning nutrition and lectures on nutrition in the afternoon which was otherwise set aside for excursions out of town. Although nothing sensationally new (no new deficiency diseases etc.) was reported, several accounts of principle significance were made. Calcano and his co-workers (Buffalo) reported that children can now be maintained in a state of nitrogen balance by parenteral administration of nitrogen and even given a surplus so that a certain reserve can be stored. The significance of fats was illustrated by Ariztia, (Santiago, Chile) who found a better increase in weight in undernourished children on a diet rich in fat than on an iso-caloric diet with less fat, and Arild E. Hansen and his co-workers (Galveston, U.S.A.) presented further experiments of feeding infants with varying quantities of unsaturated fatty acids. It can hardly be stated that his data permits any final conclusions but, in any case, it is certain that the proportion of the unsaturated fatty acids

in the diet has a definite influence upon the fatty acids in the serum and the experiments presented also revealed that the trials with the diets with the lowest fat contents had actually to be abandoned because the condition of the children was so poor that the study could not be completed. Obesity and overnourishment was discussed partly under the main heading of nutrition and also in groups with a psychological-psychiatric orientation. It was surprising to hear the pessimism expressed as regards the possibilities for reducing really overweight children. It was recognized that the families in which genuine obesity occurs have such ingrained and unfortunate dietary habits that these influence the treatment. Further, there has been an obvious regression in the belief that the caloric content of the diet is the most important factor in the question of obesity, and more and more weight is being attached to the question of muscular activity in this connection.

J. Melchior: Neurology.

There were numerous neurological lectures at the Congress in Montreal. There were no main subjects but investigation of the newly born infant occupied a prominent place and this was demonstrated in the form of films which were, by and large, identical and which did not reveal anything new for paediatricians from Denmark. Some individual lectures may be mentioned, for example, a lecture on the classical question of how to establish the diagnosis of mongolism in a child of the mongolism race? This proved to be just as difficult as might be expected. Another paper stressed the bilirubin values in premature infants and maintained that the limit must probably be established as approximately 15 mg % and in any case 20 mg %; the latter value usually being accepted as not too high a level. Although the neurological papers were not remarkable, several papers in the neurosurgical section were of greater interest: Spitz of Philadelphia presented 1100 patients

suffering from hydrocephalus (but with no tumours) and followed-up during the years 1948 to 1958. Among 300 non-operated cases only four survived with a normal I.Q. while out of 500 submitted to operation by the old shunt methods, 122 survived with good I.Q.s. The remaining 300 cases which had been operated upon according to the most recent methods with anastomosis to the venous circulation will probably show even better results. Spitz drew the careful conclusion that non-operated patients did not show better results. Sayers of Ohio presented a completely new point of view on the treatment of myelo-meningocele. These cases were treated as emergencies and submitted to operation within the first 24 hours of life. The immediate mortality fell in the group submitted to active treatment. Sayers had the impression that there were fewer severely handicapped patients than might be anticipated.

Jørgen Flamand Christensen: Cystic Fibrosis of the Pancreas.

Cystic Fibrosis of the pancreas presents a very serious problem in U.S.A. It is the second greatest cause of death among children and affects one child in 600-1000. It is considered that 5-15 per cent of the population carry the pathogenic gene. At a valuable round-table conference concerning the diagnosis and treatment the anomaly of sweating was emphasized as the most constant symptom and its demonstration as the most accurate diagnostic method. The calorie-saving effect of treatment with pancreatin and the significance of early and continual treatment of the pulmonary symptoms were discussed. The National Cystic Fibrosis Research Foundation has as its main object medical research and public education. This institute, therefore, publishes popular articles containing information about the symptoms and the course of the disease in a very realistic manner in order to get parents to be aware of the disease and to seek medical advice early in order to have the diagnosis confirmed or refuted. Such a realistic propaganda is not recommended in Denmark and

the majority here will probably consider that it is the doctor's and not the parents' responsibility to establish such a serious diagnosis. This is probably easier to carry out in Denmark because of the routine health investigations.

E. Ryssing: Allergy.

Follow-up investigation of a group of asthmatic children from The Clinic for Allergy, Montreal Children's Hospital, showed that after treatment with hyposensitization for three years 46 per cent had no asthmatic symptoms while the incidence of symptoms was high in cases in which treatment had been inadequate. The age distribution and the period of observation was not uniform in the groups. McLaren & Haber presented a study of the vital capacity and "maximal breathing capacity" in 25 asthmatic children. The values found were lower than in normal children and no changes occurred during treatment with hyposensitization. This result contrasts with the investigations which were undertaken by S. Kræpelien who found improvement of pulmonary function following adequate hyposensitization.

Rob. Usher investigated metabolic disturbances in premature infants with "respiratory distress syndrome" and found that in the first 6-12 hours respiratory acidosis was present with reduced pH (as low as 7.10) and raised $p\text{CO}_2$ (up to 6 vol %) and, in addition, low total serum protein. Thereafter, metabolic acidosis developed with falling serum bicarbonate, rising serum phosphorus and serum potassium. He therefore treated the infants with a solution containing glucose and sodium bicarbonate administered by intravenous drip for 24-48 hours. In this manner, the blood chemistry was normalized in the surviving patients. Out of 56 untreated cases, 31 died and out of 29 treated cases only three died.

K. Wilken-Jensen: Education in Paediatrics.

The education of medical students was discussed first. In the U.S.A. this takes

place mainly on the wards where the students are on duty under the leadership of a doctor. They admit patients both day and night, and are regularly examined, e.g. during the ward rounds where they demonstrate the patients in the course of vivacious discussion. They learn to talk to the parents, to which great importance is attached, and their teachers become thoroughly acquainted with their knowledge. The examination does not involve any particular difficulties, but it has proved a problem to obtain an evaluation and a standardized type of examination, and finally the question was referred to a committee. The next point was the requirements for specialist education. A specialist in the U.S.A. must, in addition to his final professional examination and compulsory year of hospital housemanship, have served for two years in a recognized paediatric department and for two years in more specialized paediatrics or paediatric practice or a combination of these. Two competent paediatricians must recommend the applicant in writing, after which he appears for a written examination which is held annually in various places in the country. At this examination, the applicant must complete a form with approximately 100 questions of very varying nature but constructed either, so that the answers yes or no suffice, or, even more frequently, so that a cross is placed at the answer considered to be correct. An examination committee reviews the papers and names the candidates who may appear for an oral examination which is held 4-6 times annually in various places. The result of the questionnaire is not reported in advance but is included in the final evaluation and if an applicant fails in the oral examination it is not necessary to repeat the written examination unless he is advised to improve his result there as well. It is a great problem to find people who can afford the time to formulate the questions as well as review the replies and hold the oral examinations.

F. Tudvad: Nephrosis.

Nothing particularly new appeared as regards nephrosis. An exhibition showed a statistical comparison between the time of survival for cortisone-treated and non-cortisone-treated cases with statistically better results in the former group. The impression was gained from conversations that treatment had not yet attained a position of general acceptance. Both prednisone and ACTH were employed in varying dosages and for varying periods but the tendency appeared to be to employ large doses for long periods, frequently commencing with continual treatment for 2-4 weeks and continuing with intermittent treatment either until the urinary and blood chemistry had returned to normal; or, in some centres, for up to a year.

Svend Erik Nielsen & J. Melchior: Congress on Mental Retardation.

After the International Paediatric Congress in Montreal, the First International Medical Conference on Mental Retardation was held in Portland, Maine. Six hundred delegates were assembled at the first meeting of this type and 35 lecturers presented oligophrenia in all of its medical aspects, particularly those of brain pathology and biochemistry. Special interest was shown at this meeting in phenylketonuria and other enzymatic defects which are associated with oligophrenia. The meeting gave an excellent all-round orientation on the subject and was good evidence of the great and increasing interest shown in oligophrenia by many research groups. It was decided to hold another meeting in Vienna in the summer of 1961.

Nocturnal Enuresis and its Treatment with a "Conditioning" Apparatus.

A. Biering: Paediatric View Points.

The age at which cleanliness in respect to nocturnal urination is attained varies greatly. At the age of four years, probably 15-20 per cent of children are still wet and at the age of seven years less than eight per

cent of boys and four per cent of girls are still wet. Less than one per cent of adults have enuresis. It is not justifiable to draw arbitrary age limits and state that children who are wet at night after such-and-such an age are not normal. Seen from a "cultural" point of view, enuresis is a product of civilization and is not found in primitive communities where children do not wear pants and sleep on a pile of straw. Enuresis is, thus, not a disease nor an abnormality but a social handicap. There is a pronounced familial predisposition and frequent coincidence with (other) phenomena of immaturity (deep sleep, frequent micritrition during the day, emotional immaturity, and certain EEG changes) while coincidence with nervous symptoms is less striking and is observed particularly with secondary enuresis. Conditioning treatment which is carried out by means of an electric bell which rings when urine wets a pair of electrodes under the sheet must be interpreted as a training of new reflex pathways. Out of 21 children treated with this apparatus 12 were dry every night on follow-up examination six months after treatment. Three patients were wet once or twice a month and six remained unchanged or only slightly improved.

Inger Jespersen: Psychological Points of View.

It is a great handicap for a child to be a "bedwetter". It is important to obtain a complete picture of the repercussions between the members of the family and of the child's own conception of the situation. There is no particular problem complex characteristic for enuresis but usually conflict situations are present where children with secondary enuresis are concerned and this may be regarded as parallel to psychosomatic conditions. If the demands of cleanliness are introduced at a time when the child is not sufficiently mature the seed of a state of conflict between mother and child may be sown and may result in enuresis among other things. On the other hand, the child may become adjusted to the wet bed so that an apathetic situation results. Psychological

treatment of children with enuresis does not reveal any definite relationship between the effect on the psyche and on the enuresis. As an example, the case of a boy is mentioned. In this child the enuresis relapsed following a brief good effect of treatment with the apparatus. Following psychological treatment with good effect on the psychic symptoms but not on the enuresis, renewed treatment with the apparatus gave a prolonged good result. In a diagram with columns, the relationship of the results of treatment after a period of observation of six months to the age, sex, maturity, I.Q., type of personality, general psychic condition, adjustment to the environment, and the type of the enuresis (primary or secondary) were demonstrated. No psychic trauma could be demonstrated resulting from the treatment; rather, there was a tendency to improvement.

DISCUSSION: *F. Gjedde & E.-M. V. Wel-ling:* Nine patients, of whom the majority had not reacted to medical treatment, were treated with a conditioning apparatus consisting of an electric bell which rings when micturition occurs in the bed. Of these, five patients became totally or nearly completely dry after treatment for a couple of months while the remaining four patients returned the apparatus as the parents said they either could not make it work or could not stand the noise. — *E. Tudvad:* In the Children's Hospital, Fuglebakken, Copenhagen, we have done a considerable amount of work to elucidate the environmental conditions as thoroughly as possible, both by means of medical information and from social reports and psychological investigations, and by means of a series of conversations with the parents. The treatment of enuresis apart from admission to hospital was, by and large, limited to lifting; once, at the usual bedtime. The results are not very encouraging. — *P. W. Bræstrup:* It is rather disappointing that the results do not appear to be decidedly better than those obtained by much less time-consuming advice of an ordinary nature, and that despite the fact that the

very detailed psychological investigation may act therapeutically and advisably, the results cannot compare with the effect of the electric bell apparatus alone. — *K. Wilken-Jensen*: Expressed gratitude for the lectures and set two questions: 1) Can any conclusions be drawn from the results demonstrated? 2) In evaluating the results obtained, has any consideration been taken of whether the apparatus was employed in summer or in winter? Summer nights are so much shorter that there is less time to wet the bed in. — *J. Vesterdal*: Evaluation of the efficacy of the treatment is rendered difficult by the fact that enuresis is affected by suggestion. The material presented is too limited for any statistical conclusions to be drawn regarding the relationship between the psychic constitution etc. and the results of treatment. — *E. Ryssing*: Cystometric investigations which I undertook some years ago suggest that there was perhaps one or other physiological abnormality in children with enuresis. In many enuretic children, variations in pressure occurred on slight filling of the bladder. As a rule, the maximal bladder volume did not deviate from the normal. — *S. Heinild*: Enuresis cannot, as a rule, be regarded as a nervous phenomenon or as a sign of unfortunate environmental conditions. Late maturation or development in this particular respect appear to be concerned. Investigations concerning the mechanism involved are, naturally, always of value. — *A. Biering*: To Dr Flamand Christensen: according to Klackenberg's investigations, there is no relationship between the time at

which "toilet training" is commenced and the time at which the children become dry. To Dr Tudvad: the period of observation is of great significance for the results. The longer the period of observation, the better are the results because a certain number of children become dry spontaneously. To Dr Øster: when, as a school medical officer, one meets parents whose child is wet at night but who accept this as a fact so that there is no problem, I would not propose any treatment as we cannot promise a good result with 100 per cent certainty. These are frequently parents who themselves have had enuresis. To Dr Wamberg: there is nothing to hinder the general practitioner undertaking the treatment if only he is prepared to offer the necessary time for instruction and to correct the errors which parents may make in treatment. When the leads are connected to the isolated part of the tinfoil, it is obvious that the apparatus will not function, but not all parents are familiar with elementary electricity. — *Inger Jespersen*: To Dr Bræstrup: the 20 hours of psychological treatment employed for each child indicate working hours and part of the time was devoted to reviewing tests and conversations with parents and school authorities. Even the contact with the child was limited to the conversations absolutely necessary for the psychological investigation. To Dr Henriques: the material has not been summed up with regard to children only, but this can easily be done.

Folke Tudvad, Copenhagen

The Pediatric Society of South Sweden

Meeting, October 25, 1959

Ivar Nilsby: Constitutional anemia with multiple malformations (Fanconi's syndrome)

In 1927 Fanconi described 3 siblings with the combination of anemia and congenital malformations. Since then a number of simi-

lar cases have been reported. They are characterized by an anemia with macrocytosis in combination with deformities, which arranged in the order of frequency are: (1) increased pigmentation of the skin, (2) hypogenitalism, (3) dwarfism, (4) microcephaly, (5) anoma-

lies of the thumbs, (6) strabismus, (7) renal defects and (8) congenital heart disease. The anemia generally does not appear before 3 years of age. At the same time thrombocytopenia and leukopenia always occur. The anaemia is progressive and always fatal. The etiology is unknown. A hereditary factor has been discussed and in such a case a recessive trait is suggested. Effective treatment is lacking. Repeated blood transfusions can prolong life to some extent. The following 3 cases were siblings. The parents were cousins.

Case 1: Girl; died of uremia at 6 years of age. She exhibited dwarfism, pigmented skin, malformation of the thumbs, renal defects and a moderate anemia.—*Case 2:* Girl; died of anemia at 8 years of age. She exhibited dwarfism, pigmented skin, malformation of the thumbs and hyperchromic anemia with leukopenia and thrombocytopenia.—*Case 3:* Boy; died of anemia at 6 years of age. He exhibited dwarfism, pigmented skin, malformation of the thumbs and hyperchromic anemia with leukopenia and thrombocytopenia.

R. Thelin: Two cases of Laurence-Moon-Biedl-Bardet's syndrome

Case 1: Boy; born April 30, 1952. Several cases of polydactylism and other malformations in the father's family. Weight at birth 5300 g, at 6 years 47.1 kg and at 7 years 55 kg. Both hands have 6 fingers and both feet 6 toes. There is syndactylism in several places. The legs and feet are very clumsy. The patient was operated on for luxatio gen. dxt. congenit. Other symptoms are oxycephaly, exophthalmus and hypertelorism. The ophthalmic examination shows the disc margins only slightly blurred. No signs of retinitis pigmentosa. Normal ERG. Cryptorchism. Normal excretion of 17-KS as well as other laboratory values. Terman-Merrill test showed an I.Q. of 65.—*Case 2:* Girl; born August 26, 1957. No hereditary data of interest. An extra toe was removed the day after birth. Somewhat delayed speech development. She began to walk at 1½ years but did not speak clearly until 8 years of age. Weight

at 1 year 15.7 kg, at 3 years 32 kg and at 7 years 40 kg. She has difficulty in seeing in the dark. Ophthalmic examination shows a typical retinitis pigmentosa with a completely absent ERG. In addition strabismus and astigmatism are present. Terman-Merrill test showed an I.Q. of 72. Blood cholesterol 358 mg %. Normal blood sugar with a delayed drop of blood sugar in glucose tolerance test. On one occasion increase of corticosteroid excretion but later normal values. Roentgen examination of hand skeleton reveals unusually broad middle and outer phalanges of the little finger of the left hand with a central defect in the outer phalanx, probably a malformation.

The classic tetrad of Laurence-Moon-Biedl-Bardet's syndrome is the following: (1) retinitis pigmentosa, (2) mental retardation, (3) poly- and syndactylism and (4) obesity with hypogenitalism and cryptorchism. In 1949 Brattgård found 300 published cases, but since then only a few cases have appeared in the literature. In Sweden Kaijser described 4 cases in 1957. The syndrome is not always complete and not always limited to the classic symptoms. Sometimes there is oxycephaly as well as diabetes insipidus, dwarfism, deafness, etc. Heredity has also been considerably discussed, and most authors seem to agree that the syndrome is hereditary and is inherited recessively. Of our 2 cases the girl is a so-called complete case, but here heredity is lacking. The boy lacks retinitis pigmentosa but has instead oxycephaly and malformation of the lower extremities and has a distinct heredity for defects from his father's side, especially polydactylism. According to the available literature ERG examinations have not been performed earlier on patients with this syndrome. These were carried out at the Ophthalmologic Clinic of the Caroline Hospital in Stockholm (Docent Sundmark).

S.-I. Björklund: Leydig cell tumor

A 6½-year-old boy, who had grown rapidly in the past year, exhibited marked enlargement of the penis and growth of pubic hair. The child was 145 cm tall and weighed 32 kg.

The penis was of adult appearance with a moderate growth of pubic hair, but there was no axillary hair or beard. On palpation the prostate gland felt like that of (about) a 17-year-old. In the left testis a tumor about half the size of a hazel nut was palpated. Roentgen examination showed a skeletal age of about 15 years. Tests for cholesterol, PBI and glucose tolerance were normal. The tumor was extirpated and the PAD was interstitial cell tumor with no evidence of malignancy. On histologic examination it could not be determined whether the tumorous tissue was composed of interstitial cells or aberrant adrenocortical tissue.— Since the operation the patient has been examined several times. Eleven months afterwards the boy was 156 cm tall. The previously deep voice had become somewhat higher. Prior to the operation the patient presumably masturbated but stopped after the operation. The secondary hair growth and size of the penis were unchanged. Hormone analysis prior to operation showed: high normal values for 17-KS and pathologically high values for dehydroisoandrosterone and androsterone, FSH < 10 m.u. (mouse units), estrogenic substances < 25 m.u.—Normal excretion of 17-KS, dehydroisoandrosterone and androsterone after the operation. In the recent literature the hypothesis has been advanced that the so-called interstitial cell

tumors with pubertas praecox are actually composed of aberrant adrenocortical tissue. The case described above cannot absolutely settle the question, but the fact that the excretion of dehydroisoandrosterone (which is considered to be formed only in the adrenal cortex) decreased after the operation favors the view that the extirpated tumor was adrenocortical tissue.

Rigel Quiding-Boström: Incontinentia pigmenti

A full-term girl at 3 days of age developed a rash over her entire body in the form of palm-sized, reddened, elevated efflorescences, which after a few weeks were followed by vesicles and later by hard, keloid-like, dark-pigmented formations. Marked eosinophilia in the blood. The PAD of the hard efflorescences showed signs of the pigment anomaly which is called incontinentia pigmenti or Bloch-Sulzberger's disease. Since the discovery of the disease in 1925 some 80 cases have been reported. The disease is usually associated with defects in the skeleton, eyes and central nervous system with retarded development of the teeth, hair and nails. Its occurrence is familial and affects mostly women. The etiology is unknown. The cutaneous changes have a good prognosis.

ANNOUNCEMENT

First International Conference on Congenital Malformations

The International Medical Congress Ltd., which has strong affiliation with the National Foundation of New York, is holding its First International Conference on Congenital Malformations in London from 18–22 July, 1960. *General Chairman* PROF. J. D. BOYD (England).

CORRESPONDENCE AND INQUIRIES—regarding the Conference should be addressed to the Secretariat of the First International Conference on Congenital Malformations, 67 New Bond Street (Dering Yard), London, W.1, England. Telegrams: Conmal Wesdo London. Cables: Conmal London.

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